

11/13/00

Box Seq.

A

11/10/00

USPTO

**TRANSMITTAL OF  
UTILITY  
APPLICATION  
UNDER 37  
C.F.R. §1.53**

Attorney Docket No.

24737-1906C

First named inventor

Kalyanaraman Ramnarayan

Express mail label #

EL675147108US

Date of mailing

November 10, 2000

09/709905

11/10/00

**Application Elements**

1. ☒ Fee Transmittal Form
2. ☒ Specification containing 97 pages (including claims and Abstract) and a sequence listing containing 194 pages.
  - a. Title: **USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS FOR DRUG DESIGN AND CLINICAL APPLICATIONS**
  - b. Number of claims: 66
3. ☒ 46 sheets of drawings with 11 Figs.
4. ☐ Unexecuted Declaration listing name of inventor
5. ☒ Sequence Listing
  - ☒ Paper copy (identical to computer copy)
  - ☒ Computer readable copy
  - ☐ Verified statement

**Accompanying Application Papers**

6. ☐ Copy of assignment from prior application
7. ☐ Preliminary Amendment
8. ☒ Two identical CD-ROM disks containing Tables 4 and 5, Machine format: IBM-PC, Operating System: MS-Windows, File Names:  
1906CTAB.001, 59,538 KB, created 11/10/00,  
1906CTAB.002, 304 KB, created 11/10/00, and  
1906CTAB.003, 11,413 KB, created 11/10/00.
9. ☒ Special Information:  
Table 4 is contained in files 1906CTAB.001 (part 1) and 1906CTAB.002 (part 2),  
Table 5 is contained in file 1906CTAB.003.
10. ☒ Return Receipt Postcard

**SIGNATURE OF ATTORNEY/AGENT**

HELLER EHRMAN WHITE &amp; McAULIFFE LLP

Stephanie Seidman

Registration Number: 33,779

☒ Benefit of priority claimed under 35 U.S.C. §120 to U.S. application Serial No. 09/438,566, filed November 10, 1999 (continuation-in-part) and to Atty. Dkt. No. 24737-1906B, filed November 1, 2000 (continuation-in-part).

**CORRESPONDENCE ADDRESS**

NAME

Stephanie Seidman  
Registration No. 33,779  
Heller Ehrman White & McAuliffe LLP

Address

4250 Executive Square, 7th Floor, La Jolla, CA 92037

Telephone: 858/450-8400

Facsimile: 858/587-5360

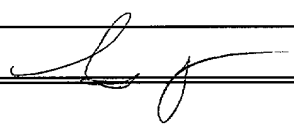
<b>FEE TRANSMITTAL ACCOMPANYING UTILITY APPLICATION UNDER 37 C.F.R. §1.53</b>	Attorney Docket No.	24737-1906C
	First named inventor	Kalyanaraman Ramnarayan
	Express mail label #	EL675147108US
	Date of mailing	November 10, 2000

#### FEE CALCULATION FOR CLAIMS

a)	Basic Fee		\$ 710.00
b)	Independent Claims $\frac{8}{66} - 3 = \frac{5}{46}$	$\times \$ 80.00$	\$ 400.00
c)	Total Claims	$\frac{46}{66} \times \$ 18.00$	\$ 828.00
d)	Fee for Multiple Dependent Claims -	\$270.00	\$ 0.00
<b>TOTAL FILING FEE</b>			<b>\$ 1938.00</b>

Status as Small Entity:  
☐ is claimed.  
☒ is not claimed.

- [X] A check in the amount of \$1938.00 to cover the fee for filing the application.
- [ ] Charge \$ .00 to Deposit Account No. 50-1213
- [X] The Commissioner is hereby authorized to charge any fees that may be required in this application under 37 C.F.R. §§ 1.16-1.17 during its entire pendency, or credit any overpayment, to Deposit Account No. 50-1213. If proper payment is not enclosed, such as a check in the wrong amount, unsigned, post-dated, otherwise improper or informal, or absent, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-1213 during the entire pendency of this application. This sheet is filed in duplicate.

CORRESPONDENCE ADDRESS					
NAME	Stephanie Seidman Registration No. 33,779 Heller Ehrman White & McAuliffe LLP				
Address	4250 Executive Square, 7th Floor, La Jolla, CA 92037				
	Telephone: 858/450-8400			Facsimile: 858/587-5360	
Submitted by:					
Typed or printed name	Stephanie Seidman			Reg. Number	33,779
Signature			Date	11/10/00	Deposit Account
					50-1213

00700405-11000

# USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS AND CLINICAL APPLICATIONS

## RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Serial No. 09/438,566 to Kalyanaraman Ramnarayan, Edward T. Maggio and P. Patrick Hess, filed November 10, 1999 entitled "USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS FOR DRUG DESIGN AND CLINICAL APPLICATIONS"; and U.S. application Serial No. (Attorney Dkt. No. 24737-1906B) to Kalyanaraman Ramnarayan, Edward T. Maggio and P. Patrick Hess, filed November 1, 2000, entitled "USE OF COMPUTATIONALLY DERIVED PROTEIN STRUCTURES OF GENETIC POLYMORPHISMS IN PHARMACOGENOMICS FOR DRUG DESIGN AND CLINICAL APPLICATIONS." U.S. application Serial No. (Attorney Dkt. No. 24737-1906B) is a continuation of U.S. application Serial No. 09/438,566. The above-noted applications are incorporated by reference in their entirety.

## **Incorporation by reference of Tables provided on Compact Disks**

An electronic version on compact disk (CD) ROM of Tables 4 and 5, which set forth coordinates for three-dimensional structures of proteins in the database described herein is filed herewith. The contents thereof is incorporated by reference in its entirety. Table 4 is the HIV reverse transcriptase coordinates, and Table 5 is the HIV protease coordinates. The files that contain Table 4 are entitled 1906CTAB.001 and 1906CTAB.002, created on November 10, 2000, and are 59,538 kilobytes and 304 kilobytes, respectively. The file that contains Table 5 is entitled 1906CTAB.003, created on November 10, 2000, and contains 11,413 kilobytes.

## FIELD OF THE INVENTION

The present invention is related to computer-based methods and relational databases that use three-dimensional (3-D) protein structural models derived from genetic polymorphisms in the areas of computer-assisted drug design and the prediction of clinical responses in patients.

## BACKGROUND OF THE INVENTION

Recent advances in molecular biology, such as the discovery and identification of large numbers of genes and the sequences thereof encoded in the genomes of humans, other mammals and infectious disease agents, have contributed to the identification of a large number of proteins, biological receptors and other macromolecules and complexes that are promising therapeutic targets. Based on the information derived from the gene sequences, the three-dimensional (3-D) molecular structures of the corresponding target proteins or receptors can be determined.

Since 3-D protein structure is related to biological function, structure-based drug design is an increasingly useful methodology that has made a great impact in the design of biologically active lead compounds. Drug designers can design and screen potential new drugs via computational methods, such as docking or binding studies, before actually beginning patient testing. These experiments can be performed *in silico* at a tiny fraction of the clinical cost.

The resulting molecules, while serving as lead compounds, often have unpredictable effects when employed in clinical trials. In addition, it has been observed that existing drugs with known clinical efficacy far often fail to achieve beneficial results when given to particular patients, or particular subpopulations, such as ethnic groups, of patients. Genetic stratification of a population can be the difference between drug failure and drug approval. Hence there is a need to develop methods to improve the drug discovery process. Therefore, it is an object herein to provide, among a variety of benefits, methods and products that address



and solve these problems. In particular, it is an object herein to provide computationally-based methods for drug design, clinical testing protocols, identification of new drug candidates and drug therapies; for predicting drug sensitivity and resistance and other methods.

### **SUMMARY OF THE INVENTION**

Provided herein are computer-based methods for generating and using three-dimensional (3-D) structural models of target biomolecules, particularly polymorphic and allelic variants. Also provided herein are databases that contain the sequences of such variants and also the 3-D structure of the variants for use with the methods.

Genetic polymorphisms arise, for example, as a result of gene sequence differences or as a result of post-translational modifications, including glycosylation. Hence genetic polymorphisms are manifested as gene products and proteins having variant structures. The variant structures result in differences in biological responses among the originating organisms. These differences in response, include, but are not limited to, differences among patient responses to a particular drug, effective dosage differences, and side effects. With respect to infectious organisms, some polymorphisms may arise that convey resistance or susceptibility to particular drug therapies by the altering the drug target structure.

Structural changes that arise as a result of genetic polymorphisms are not of unlimited variety, since 3-D structure impacts upon function. A knowledge of the repertoire of the fine differences among generally similar 3-D structures of particular proteins will permit design of drugs that bind to the most polymorphisms, drugs that induce the fewest side-effects, and drugs that are more effective against infectious agents. Knowledge of these structures ultimately will permit patient-specific or subpopulation-specific, such as ethnic, age, or gender groups, design or selection of drugs.

The methods that are provided are for determining and using 3-dimensional (3-D) protein structures that are derived from genetic polymorphisms to understand differences in biological activity that result from the polymorphisms, and to use this understanding to aid in the identification of potential new drug candidates and drug therapies. Also provided are methods for analyzing 3-D structures of protein structural variant targets derived from genetic polymorphisms to identify common structural features among the variants; methods for identifying structural changes in target proteins that are associated with multiple mutations arising from genetic polymorphisms and correlating this information with biological activity; methods for using clinical data in conjunction with structural variants derived from genetic polymorphisms to understand and predict the pharmacological effects and clinical outcomes for drugs or potential drugs. Also provided are methods for generating 3-D protein structures derived from a given genotype to analyze protein-drug binding *in silico* to predict drug sensitivity or resistance. Also provided are databases that are used in methods provided herein and methods for generating the databases.

In particular, target biomolecules are protein structural variants encoded by genes containing genetic variations, or polymorphisms. 3-D models of the structures of proteins are determined. The models are generated using molecular modeling techniques, such as homology modeling. The resulting models are then used in the methods provided herein, which include structure-based drug design studies to design and identify drugs that bind to particular structural variants; structure-based drug design studies and to predict clinical responses in patients; and to design drugs that bind to all or a substantial portion of allelic variants of a target, to thereby increase the population of patients for whom a particular drug will be effective and/or to decrease the undesirable side-effects in a larger population.

Hence, computer-based methods of drug design based on target protein structural models derived from genetic polymorphisms are provided. The methods involve obtaining one, preferably two or more amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, where sequences represent different genetic polymorphisms, and generating 3-D protein structural variant models from the sequences. Structure-based drug design techniques are used to design potential new drug candidates or to suggest modifications to existing drugs based on predicted intermolecular interactions of the drugs or drug candidates with the models. Alternatively, drug molecules can be computationally docked with 3-D protein structural variant models based upon the sequences and energetically refined before performing structure-based drug design studies.

In preferred embodiments, binding interactions between a drug or potential new drug candidate molecules and the structural variants are calculated in order to optimize intermolecular interactions between drug or potential drug molecules and the structural variant models or to select drug therapies for patients by determining a drug or drugs that have favorable binding interactions with the structural variant models.

In other embodiments, the binding interactions are determined by calculating the free energy of binding between the protein structural variant model and a docked molecule; and decomposing the total free energy of binding based on the interacting residues in the protein active site.

After the protein structural variant models are generated, selected model structures are analyzed to determine common structural features that are conserved throughout the selected models. The conserved structural features can serve as scaffolds or pharmacophore models into which potential drugs or modified drugs are docked. For example, the selected model structures may represent the structural variants resulting from the most commonly occurring genetic polymorphisms or from

genetic polymorphisms found in a specific patient subpopulation, such as a particular age group, ethnic or racial group, sex, or other subpopulation. Alternatively, the models may be selected based on clinical information, for example, the structural variants may be derived based on patients receiving a specific treatment regimen or exhibiting a particular clinical response to a given drug or on the duration of a particular drug treatment.

The methods provided herein can be used for predicting clinical responses in patients based on genetic polymorphisms. For example, a structural variant model derived from a subject, such as a human patient, exhibiting a particular genetic polymorphism is generated and screened against a number of reference protein structural variant models derived from genetic polymorphisms of the same gene in other such subjects. In certain embodiments, the reference structures are stored in a database, preferably with observed clinical data associated with the structures, or polymorphisms. The structural variant model from the subject is compared to a reference structures, for example, by database searching, in order to identify reference structural variants that are similar to the model structure derived from the subject. Based on the premise that structurally similar targets will have similar clinical responses, a clinical outcome can be predicted for the patient based on the structures identified through structural comparison or database searching. This information can also be used in the design and analysis of clinical trials; it can also be used for selecting appropriate therapies for a subject in instances in which the subject is a patient and the protein is a drug target.

The methods are also used to design therapeutic agents that are active against biological targets that have become drug resistant, particularly due to genetic mutations. In certain embodiments, 3-D protein structural variant models are generated for a target protein in which genetic mutations have occurred and against which a given drug is no longer biologically active. The models are compared to 3-D protein

structural variant models of the target protein against which the drug has biological activity in order to identify structural differences between the susceptible and resistant targets. The differences can be used to understand the structural contributions to drug resistance, and this information can be utilized in structure-based drug design calculations to identify new drugs or modifications to the existing drug that circumvent the resistance problem.

A computer-based method for identifying compensatory mutations in a target protein is also provided. The method involves obtaining the amino acid sequence of a target protein containing multiple amino acid mutations that is expressed in a patient, where the structure of a form of the target protein that responds to a particular drug, including the active site, has been structurally characterized; generating a 3-D structural model of the mutated protein; comparing the structure of the mutated protein with the form of the protein that responds to the drug to identify structural differences and/or similarities arising from the mutations; comparing the biological activities of the drug against the mutated protein and the form of the protein that responds to the drug to determine the effects of the mutations on drug response; and identifying the mutations in the protein that affect biological activity based on the comparisons. The target biomolecules can also be used in a method referred to herein as computational phenotyping to predict drug sensitivity or resistance for a given genotype. These computer-based method for identifying phenotypes *in silico* are provided. The methods involve obtaining from a patient/specimen, such as a body fluid or tissue sample, including blood, cerebral spinal fluid, urine, saliva, sweat and tissue samples, the amino acid sequence of a target protein; generating a 3-D structural model of the target protein; performing protein-drug binding analyses; and predicting drug sensitivity or resistance based on the protein-drug binding analyses.

Molecular structure databases containing protein structural variant models produced by the methods are also provided. The databases may also contain biological or clinical data associated with the structural variants. The databases can be interfaced to a molecular graphics package for visualization and analysis of the 3-D molecular structural models. In particular, databases containing the 3-D structures of polymorphic variants of selected target genes, particularly pharmaceutically significant genes with pharmaceutically significant gene products, such as proteases and polymerases, including reverse transcriptases, and receptors, such as cell surface receptors, are provided. The databases may be stored and provided on any suitable medium, including, but are not limited to, floppy disks, hard drives, CD-ROMS and DVDs.

Also provided are relational databases for managing and using information relating to genetic polymorphisms. The databases contain 3-D molecular coordinates for structural variants derived from genetic polymorphism, a molecular graphics interface for 3-D molecular structure visualization, computer functionality for protein sequence and structural analyses and database searching tools. The databases may further include observed clinical data associated with the genetic polymorphism. The databases provide a means to design the allele-specific drugs and also to identify among alleles common or conserved structural features that can serve as the target for drug design.

The databases can also be used for identification of invariant residues and regions of a target biomolecule, such as an HIV protease or reverse transcriptase. The identified invariant regions are then used to computationally screen compounds, preferably small molecules by assessing binding interactions. The compounds so-identified serve as candidates for drugs that will be effective for a larger proportion of a population or against a broader range of variants of a pathogen, where the target protein is from a pathogen.

Systems, including computers, containing the databases also are provided herein. Any computer known to those of skill in the art for maintaining such databases is contemplated. User interfaces for accessing and manipulating the databases and content thereof are also provided.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

**FIG. 1** illustrates a method for creating a protein structural variant relational database.

**FIG. 2** is a flow chart that describes one method used to generate structural variant models derived from genetic polymorphisms and to use the models in structure-based drug design studies.

**FIG. 3** is a flow chart that describes an alternative method used to generate structural variant models derived from genetic polymorphisms and to use the models in structure-based drug design studies.

**FIG. 4** shows the correlation between experimental and calculated changes of binding energy upon ligand modifications in the binding site of NS3.

**FIG. 5** shows a comparison of calculated *versus* experimental binding free energy changes for complexes of the tumor necrosis factor (TNF) receptor with different inhibitors.

**FIG. 6** shows the HIV PR inhibitors approved by the FDA.

**FIG. 7** shows the frequency versus amino acid residue plot of HIV PR.

**FIG. 8** shows frequency analysis of 10591 HIV PR Sequences, where ResNum is the residue number; TotOcc is the total occurrence of the mutation; Dist is the distance of the mutating residue from approximate center of active site (Asp28); WtAA is the amino acid in the wild type protein; NumMut is the number of mutations; and MutList is a list of amino acid mutations.

**FIG. 9** is a block diagram of an exemplary computer.

**FIG. 10** is a graphical representation of a relational database.

**FIG. 11** is a tabulation of the 3-D coordinates of a representative entry in a database that includes 3-D structures.

## **DETAILED DESCRIPTION OF THE INVENTION**

- A. Definitions**
- B. Computer-based methods of drug design based on genetic polymorphisms**
  - 1. Methods for obtaining amino acid sequences of a target protein
  - 2. Generation of 3-D protein structural variant models
    - a. Homology Modeling
    - b. Ab initio generation of 3-D structures
    - c. Crystal structures
  - 3. Use of 3-D structural variant models in drug design
    - a. Selection of relevant structural variants
    - b. Drug design
    - c. Computational docking
    - d. Free energy of binding studies
- C. Applications of computer-based methods**
  - 1. Genetic polymorphisms and structure-based drug design
  - 2. Drug resistance
  - 3. Identification of conserved structural features or pharmacophores
  - 4. Identification of compensatory structural changes
  - 5. Clinical Applications
- D. Creation of 3-D Structural Polymorphism Databases**
  - 1. Exemplary Databases and generation thereof
  - 2. Computer systems and Database
- E. Computational phenotyping**

### **A. Definitions**

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, published patent applications and publications referred to herein are, unless noted otherwise, incorporated by reference in their entirety. In the event a definition in this section is not consistent with definitions elsewhere, the definition set forth in this section will control.



As used herein, polymorphism refers to a variation in the sequence of a gene in the genome amongst a population, such as allelic variations and other variations that arise or are observed. Genetic polymorphisms refers to the variant forms of gene sequences that can arise as a result of nucleotide base pair differences, alternative mRNA splicing or post-translational modifications, including, for example, glycosylation. Thus, a polymorphism refers to the occurrence of two or more genetically determined alternative sequences or alleles in a population. These differences can occur in coding and non-coding portions of the genome, and can be manifested or detected as differences in nucleic acid sequences, gene expression, including, for example transcription, processing, translation, transport, protein processing, trafficking, DNA synthesis, expressed proteins, other gene products or products of biochemical pathways or in post-translational modifications and any other differences manifested among members of a population. A single nucleotide polymorphism (SNP) refers to a polymorphism that arises as the result of a single base change, such as an insertion, deletion or change in a base.

A polymorphic marker or site is the locus at which divergence occurs. Such site may be as small as one base pair (an SNP). Polymorphic markers include, but are not limited to, restriction fragment length polymorphisms, variable number of tandem repeats (VNTR's), hypervariable regions, minisatellites, dinucleotide repeats, trinucleotide repeats, tetranucleotide repeats and other repeating patterns, simple sequence repeats and insertional elements, such as Alu. Polymorphic forms also are manifested as different mendelian alleles for a gene. Polymorphisms may be observed by differences in proteins, protein modifications, RNA expression modification, DNA and RNA methylation, regulatory factors that alter gene expression and DNA replication, and any other manifestation of alterations in genomic nucleic acid or organelle nucleic acids.

As used herein, structural variants proteins refer the variety of 3-D molecular structures or models thereof that result from the polymorphisms. These variants typically arise from transcription and translation of genes containing genetic polymorphisms, but also include differentially glycosylated or otherwise post-translationally modified variants that potentially exhibit differential interactions with drugs and drug candidates.

As used herein, binding interactions refer to atomic or physical interactions between molecules including, but not limited to binding free energy, hydrophobic interactions, electrostatic interactions, steric interactions and other interactions that are commonly considered by those of skill in the art to determine the affinity of one molecule to bind to another. Favorable binding interactions refer to binding interactions that promote physical or chemical associations between molecules.

As used herein, a target protein is defined as a protein that is a receptor with which drugs or other ligands, such as small molecule or peptide agonists or antagonists or other proteins or biomacromolecules, such as DNA or RNA, interact to bring about a biological response.

As used herein, structure-based drug design refers to computer-based methods in which 3-D coordinates for molecular structures are used to identify potential drugs that can interact with a biological receptor. Examples of such methods include, but are not limited to, searching of small molecule libraries or databases, conformational searching of a ligand within an active site of identify biologically active conformations or computational docking methods.

As used herein, pharmacogenomics refers to study of the variability of patient responses to drugs due to inherent genetic differences.

As used herein, computational docking refers to techniques wherein molecules, for example, a ligand and receptor or active site, are fitted together based on complementary interactions, for example, steric, hydrophobic or electrostatic interactions.

As used herein, energetic refinement refers to the use of molecular mechanics simulation techniques, such as energy minimization or molecular dynamics, or other techniques, such as quantum-based approaches, to "adjust" the coordinates of a molecular structural model to bring it into a stable, low energy, conformation. In molecular mechanics simulations, the potential energy of a molecular system is represented as a function of its atomic coordinates along with a set of atomic parameters, called a forcefield. Energy minimization refers to a method wherein the coordinates of a molecular conformation are adjusted according to a target function to result in a lower energy conformation. Molecular dynamics refers to methods for simulating molecular motion by inputting kinetic energy into the molecular system corresponding to a specified temperature, and integrating the classical equations of motion for the molecular system. During a molecular dynamics simulation, a system undergoes conformational changes so that different parts of its accessible phase space are explored.

As used herein, clinical data refers to information obtained from patients pertaining to pharmacological responses of the patient to a given drug, including, but not limited to efficacy data, side effects, resistance or susceptibility to drug therapy, pharmacokinetics or clinical trial results.

As used herein, patient histories, include medical histories and other any information, such as parental medical histories, dates and places of birth of the patient and parents, number of siblings, number of children and other such data.

As used herein, compensatory mutations are mutations that act in concert with active site mutations by compensating for functional deficits caused by changes or mutations that affect binding in the active site.

As used herein, a relational database is a collection of data items organized as a set of formally-described tables from which data can be accessed or reassembled in many different ways without having to reorganize the database tables. Such databases are readily available

commercially, for example, from Oracle, IBM, Microsoft, Sybase, Computer Associates, SAP, or multiple other vendors.

As used herein, a phenotype refers to a set of parameters that includes any distinguishable trait of an organism. A phenotype can be physical traits and can be, in instances in which the subject is an animal, a mental trait, such as emotional traits. Some phenotypes can be determined by observation elicited by questionnaires or by referring to prior medical and other records. For purposes herein, a phenotype is a parameter around which the database can be sorted.

As used herein, genotype refers to a specific gene or totality of genetic information in a specific cell or organism.

As used herein, haplotype refers refers to two or more polymorphism located on a single DNA strand. Hence, haplotyping refers to identification of two or more polymorphisms on a single DNA strand. Haplotypes can be indicative of a phenotype.

As used herein, a parameter is any input data that will serve as a basis for sorting the database. These parameters will include phenotypic traits, medical histories, family histories and any other such information elicited from a subject or observed about the subject. A parameter may describe the subject, some historical or current environmental or social influence experienced by the subject, or a condition or environmental influence on someone related to the subject. Paramaters include, but are not limited to, any of those described herein, and known to those of skill in the art.

As used herein, computational phenotyping, refers to computer-based processes that assess the phenotype resulting from a particular genotype. The phenotype describes observables, such as, but are not limited to, the structure of the encoded protein, its functional morphological and structural attributes. In particular, as contemplated herein, the phenotype that is assesed is the interaction of a protein with a particular compounds, particularly a drug. As exemplified herein, the

method provides a means to select an effective drug for a particular subjects, particularly mammals, or class thereof.

As used herein, a database refers to a collection of data; in this case data relating to polymorphic variants. Hence a database contains the nucleic acid sequences encoding the variants, or a portion of the variant, such as a portion containing the active site or targetted site. Additionally, the database may contain other information related to each entry, including but are not limited to, the corresponding 3-D structure of the encoded protein (or a portion thereof) and information regarding the source of each sequence. Some of the entries in a database may be identical, and for purposes herein, a database contains at least 2 different entries, typically far more than 2 entries. The number of entries depends upon the protein of interest and variety and number of polymorphisms that exist. Generally a database will have at least 10 different entries, typically more than 100, more than 500, more than 1000, more than 2000, 3000, 4000, 5000, 8000, 10,000, 50,000, 100,000 and greater. Databases herein containing 20,000 entries and more have been generated and are exemplified herein.

As used herein, a relational database stores information in a form representative of matrices, such as two-dimensional tables, including rows and columns of data, or higher dimensional matrices. For example, in one embodiment, the relational database has separate tables each with a parameter. The tables are linked with a record number, which also acts as an index. The database can be searched or sorted by using data in the tables and is stored in any suitable storage medium, such as floppy disk, CD rom disk, hard drive or other suitable medium.

As used herein, a profile refers to information relating to, but not limited to and not necessarily including all of, age, sex, ethnicity, disease history, family history, phenotypic characteristics, such as height and weight and other relevant parameters.

As used herein, a biopolymer includes, but is not limited to, nucleic acid, proteins, polysaccharides, lipids and other macromolecules. Nucleic acids include DNA, RNA, and fragments thereof. Nucleic acids may be derived from genomic DNA, RNA, mitochondrial nucleic acid, chloroplast nucleic acid and other organelles with separate genetic material.

As used herein, a DNA or nucleic acid homolog refers to a nucleic acid that includes a preselected conserved nucleotide sequence. By the term "substantially homologous" is meant having at least 80%, preferably at least 90%, most preferably at least 95% homology therewith or a less percentage of homology or identity and conserved biological activity or function.

As used herein, a receptor refers to a molecule that has an affinity for a given ligand. Receptors may be naturally-occurring or synthetic molecules. Receptors may also be referred to in the art as anti-ligands. As used herein, the terms, receptor and anti-ligand are interchangeable. Receptors can be used in their unaltered state or as aggregates with other species. Receptors may be attached, covalently or noncovalently, or in physical contact with, to a binding member, either directly or indirectly via a specific binding substance or linker. Examples of receptors, include, but are not limited to: antibodies, cell membrane receptors surface receptors and internalizing receptors, monoclonal antibodies and antisera reactive with specific antigenic determinants (such as on viruses, cells, or other materials), drugs, polynucleotides, nucleic acids, peptides, cofactors, lectins, sugars, polysaccharides, cells, cellular membranes, and organelles.

Examples of receptors and applications using such receptors, include but are not restricted to:

a) enzymes: specific transport proteins or enzymes essential to survival of microorganisms, which could serve as targets for antibiotic (ligand) selection;

b) antibodies: identification of a ligand-binding site on the antibody molecule that combines with the epitope of an antigen of interest may be investigated; determination of a sequence that mimics an antigenic epitope may lead to the development of vaccines of which the immunogen is based on one or more of such sequences or lead to the development of related diagnostic agents or compounds useful in therapeutic treatments such as for auto-immune diseases;

c) nucleic acids: identification of ligand, such as protein or RNA, binding sites;

d) catalytic polypeptides: polymers, preferably polypeptides, that are capable of promoting a chemical reaction involving the conversion of one or more reactants to one or more products; such polypeptides generally include a binding site specific for at least one reactant or reaction intermediate and an active functionality proximate to the binding site, in which the functionality is capable of chemically modifying the bound reactant (see, *e.g.*, U.S. Patent No. 5,215,899);

e) hormone receptors: determination of the ligands that bind with high affinity to a receptor is useful in the development of hormone replacement therapies; for example, identification of ligands that bind to such receptors may lead to the development of drugs to control blood pressure; and

f) opiate receptors: determination of ligands that bind to the opiate receptors in the brain is useful in the development of less-addictive replacements for morphine and related drugs.

As used herein, prion refers to an infectious pathogen that causes central nervous system spongiform encephalopathies in humans and animals. No nucleic acid component is necessary for the infectivity of prion protein (see, *e.g.*, U.S. Patent No. 5,808,969).

As used herein, a ligand is a molecule that is specifically recognized by a particular receptor. Examples of ligands, include, but are not limited to, agonists and antagonists for cell membrane receptors, toxins and

venoms, viral epitopes, hormones (*e.g.*, steroids), hormone receptors, opiates, peptides, enzymes, enzyme substrates, cofactors, drugs, lectins, sugars, oligonucleotides, nucleic acids, oligosaccharides, proteins, and monoclonal antibodies.

As used herein, complementary refers to the topological compatibility or matching together of interacting surfaces of a ligand molecule and its receptor. Thus, the receptor and its ligand can be described as complementary, and furthermore, the contact surface characteristics are complementary to each other.

As used herein, a ligand-receptor pair or complex formed when two macromolecules have combined through molecular recognition to form a complex.

The terms "homology" and "identity" are often used interchangeably. In this regard, percent homology or identity may be determined, for example, by comparing sequence information using a GAP computer program. The GAP program utilizes the alignment method of Needleman and Wunsch (*J. Mol. Biol.* 48:443 (1970)), as revised by Smith and Waterman (*Adv. Appl. Math.* 2:482 (1981)). Briefly, the GAP program defines similarity as the number of aligned symbols (*i.e.*, nucleotides or amino acids) which are similar, divided by the total number of symbols in the shorter of the two sequences. The preferred default parameters for the GAP program may include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov and Burgess, *Nucl. Acids Res.* 14:6745 (1986), as described by Schwartz and Dayhoff, eds., *ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Whether any two nucleic acid molecules have nucleotide sequences that are at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99%



"identical" can be determined using known computer algorithms such as the "FAST A" program, using for example, the default parameters as in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444 (1988). Alternatively the BLAST function of the National Center for Biotechnology Information database may be used to determine identity

In general, sequences are aligned so that the highest order match is obtained. "Identity" *per se* has an art-recognized meaning and can be calculated using published techniques. (See, e.g.: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exist a number of methods to measure identity between two polynucleotide or polypeptide sequences, the term "identity" is well known to skilled artisans (Carillo, H. & Lipton, D., *SIAM J Applied Math* 48:1073 (1988)). Methods commonly employed to determine identity or similarity between two sequences include, but are not limited to, those disclosed in Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo, H. & Lipton, D., *SIAM J Applied Math* 48:1073 (1988). Methods to determine identity and similarity are codified in computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, GCG program package (Devereux, J., *et al.*, *Nucleic Acids Research* 12(1):387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., *et al.*, *J Molec Biol* 215:403 (1990)).

Therefore, as used herein, the term "identity" represents a comparison between a test and a reference polypeptide or polynucleotide.

For example, a test polypeptide may be defined as any polypeptide that is 90% or more identical to a reference polypeptide.

As used herein, the term at least "90% identical to" refers to percent identities from 90 to 99.99 relative to a reference polypeptide. Identity at a level of 90% or more is indicative of the fact that, assuming for exemplification purposes a test and reference polynucleotide length of 100 amino acids are compared. No more than 10% (i.e., 10 out of 100) amino acids in the test polypeptide differs from that of the reference polypeptides. Similar comparisons may be made between a test and reference polynucleotides. Such differences may be represented as point mutations randomly distributed over the entire length of an amino acid sequence or they may be clustered in one or more locations of varying length up to the maximum allowable, e.g. 10/100 amino acid difference (approximately 90% identity). Differences are defined as nucleic acid or amino acid substitutions, or deletions.

As used herein, AMBER is a force field well known in the arts and designed for the study of proteins and nucleic acids as defined in Weiner et al. J. Comput. Chem. (1986) 7:230-252, where a modified AMBER (version 3.3) force field is a fully vectorized version of AMBER (version 3.0) with coordinate coupling, intra/inter decomposition, and the option to include the polarization energy as part of the total energy. AMBER is available in commercially available molecular modeling programs such as, but not limited to, Macromodel (Columbia University).

As used herein, ECEPP (Empirical Conformational Energies of Peptides Program) is a force field well known in the arts (US Patent No. 5,910,478; 5,846,763). ECEPP/3 refers to version 3 of this well known force field.

As used herein, QSAR refers to structure-activity relationship.

As used herein, vdw refers to van der Waals.

As used herein, RMSD refers to root mean-squared deviation.

As used herein, medical history refers to the parameters and data typically obtained by a physician when examining a subject or other such professional when examining other mammals, and includes such information as prior diseases, age, weight, height, sex and other information. For purposes, the subjects that serve as the source of the samples from which nucleic acids encoding polymorphisms are isolated, include animals, plants, pathogens and any organism that has nucleic acid that exhibits polymorphism. In this context medical history refers to information pertinent to the particular organism.

As used herein, subject history, refers to data such as locale in which the subject was born, raised or resident or visited, and parental history and other such information.

As used herein, a drug is an agent that binds to or interacts with a targeted protein. For purposes, a therapeutic agent is a drug.

**B. Computer-based methods of drug design based on genetic polymorphisms**

Methods for computer-based drug design based on genetic polymorphisms are provided. The methods includes the steps of obtaining one or more, preferably two or more, amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms; generating 3-dimensional (3-D) protein structural variant models of all or a portion of the protein from the sequences; and based upon the structures of the 3-D models, designing drug candidates or modifying existing drugs based on the predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants or portions thereof by computationally docking drug molecules with the target protein models; and then, optionally energetically refining the docked complexes; determining the binding interactions between the drug or potential new drug candidate molecules and the models by calculating the free energy of binding of the docked complexes and decomposing the total free

energy of binding based on interacting residues in the protein active site or sites deemed important for protein activity.

A variety of methods that include these steps are provided. Such methods have particular application, for example, in predicting patient responses. As noted, patients exhibit variable responses to drugs. For some patients a drug may be very beneficial and achieve a desired response; whereas for other patients, with the same disorder, the same drug will have little or no effect. It is known that individuals as well as groups of individuals exhibit a variety of genetic polymorphisms. As described herein, the presence or absence of such polymorphisms can be correlated with the variability of patient responses to drugs.

It is shown herein that by understanding how genetic polymorphisms affect 3-D protein structure of a drug target, for example, it is possible to ascertain the interaction of a particular drug with the target in a particular patient or groups of patients. Based upon this interaction, the outcome can be predicted. It will be possible to determine whether a patient will benefit from a drug or be at risk for a particular side effect. It is possible to predict these responses before exposure to the drug. These methods also permit rational design of drugs that can treat various populations or ultimately even individuals. These differences and effects can also be taken into account to design drugs that are not dependent upon a particular polymorphism.

Hence, the knowledge derived from understanding the effects of genetic polymorphisms can be used to develop and apply therapeutics more effectively, make clinical trials more successful, for example, by permitting selection of test subjects with the same polymorphism or with polymorphisms for which the drug is designed to interact effectively.

It is shown herein that it is advantageous to use 3-D molecular structures in drug design rather than to consider primary sequence alone. For example, most drugs target proteins either in the afflicted organism or in a pathogen. Disease, drug action and toxicity are all manifested at the

protein level. Although the nucleotide sequences of genetic polymorphisms might appear to be quite different, the resulting protein targets may have similar shapes and, therefore, the protein biological function might be the same. Conversely, although genetic polymorphism sequences might appear similar, the resulting proteins may have critical differences in their 3-D structures that greatly affect biological activity. Thus, use of 3-D protein structure models in such methods provide advantages not heretofor realized. Methods for generating 3-D structures are known to those of skill in the art and are also provided herein.

Once the protein target structural models have been selected, structure-based drug discovery methodologies, for example, computational screening or docking programs and methods (*e.g.*, DOCK (available from University of Ca, San Francisco; and AUTODOCK available from Scripps Research Institute, La Jolla), are used to design biologically-active compounds based on the 3-D structures of the biomolecular receptors. Using these methods, drug designers can identify and computationally rank the various potential clinical drug candidates for maximum efficacy, thereby performing drug discovery *in silico* and avoiding the tedious time and expense associated with *in vitro* drug discovery methods.

In addition to drug design applications, the information derived from studying the structures of biological targets can be used to understand and predict biological responses in patients, such as efficacy, toxicity, drug resistance and other pharmacological effects. Since human clinical trials may cost upwards of \$100-300 million, it is desirable to predict the outcome to the greatest extent possible for each prospective drug candidate so that the best prospective drug candidates are advanced to

clinical trials. As described below, methods are provided herein for selecting populations for clinical trials.

### **1. Methods for obtaining amino acid sequences of a target protein**

Any protein or gene or encoded mRNA that exhibits polymorphisms, herein referred to as the target protein, in structure is contemplated for use herein and for generating the databases as provided herein. The target protein is a protein, polypeptide, or oligopeptide that includes, but is not limited to, receptors, enzymes, hormones, prions, or any such compound with which drugs or other ligands, such as small molecules, peptide agonists, peptide antagonists, other proteins, nucleic acids and other biomacromolecules, interact to bring about a biological response. These target proteins occur in any organism, including plants and animals, eukaryotes and prokaryotes, including pathogens, such as protozoans, parasites, viruses, including DNA and retroviruses, and bacteria. The protein or gene can be one expressed in the organism, such as molecule targeted for drug interaction, or one expressed in a pathogen.

The target gene is one that exhibits polymorphisms (i.e., sequence variations among a population) and the target protein is the product of a gene exhibiting genetic polymorphisms, or sequence variations, as described herein. Any gene or protein that exhibits polymorphisms is contemplated herein. In particular, genes that encode proteins, polypeptides, or oligopeptides that are targets for drug interaction are contemplated herein. The genetic polymorphisms can occur in the genes of pathogens (*e.g.* viruses, bacteriae, and fungi), parasites, plants, animals, and humans. As such, the sequence a target protein can be obtained by the isolation and analysis of the gene or gene product in samples taken from pathogens, parasites, plants, animals, and humans, most preferably from humans.

The genes or proteins may be isolated from any source, such as animal or plant specimens, or the sequences obtained from any source, including known databases. If starting with gene sequences that include single or multiple nucleotide polymorphisms, the amino acid sequences of the translated proteins can be determined. Protein isolation and sequencing methods are well known to those of skill in the art. Alternatively, samples of the target protein can be obtained and sequenced directly from specimens. Multiple sequence analyses can be performed to determine the exact amino acid variations or mutations resulting from the genetic polymorphisms.

Amino acid sequences of target proteins can also be obtained from data banks and databases (e.g. GenBank, Swiss Prot, PIR) and from publications and other sources in which numerous polymorphisms have been identified and mapped. Samples may be obtained from, for example blood and tissue banks, nucleic acid isolated, genes selected or identified and polymorphisms can be mapped from such samples.

## **2. Generation of 3-D protein structural variant models**

After the amino acid sequences of target proteins are obtained via the means described in section 1, the 3-D structural models of the sequences of native proteins or of the protein structural variants are then determined. They can be determined through experimental methods, such as x-ray crystallography and NMR, and from structure databases, such as the Protein Databank (PDB). Moreover, 3-D structural models can be determined by using any of a number of well known techniques for predicting protein structures from primary sequences (e.g. SYBYL (Tripos Associated, St. Louis, Mo.), *de novo* protein structure design programs (e.g. MODELER (MSI, Inc., San Diego, CA) and MOE (Chemical Computing Group, Montreal Canada) and *ab initio* methods, see, e.g., U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895), homology modeling, and *ab initio* computational analysis. Homology modeling, structure determination based upon x-ray crystallographic structures, and

*ab initio* techniques and combinations of these methods are among those preferred herein.

#### a. Homology Modeling

Homology modeling is based on the relationship between protein evolutionary origin, function and folding patterns. Proteins of related origin and function have conserved sequences and structural features among the members of a homologous family. Using these relationships, a three-dimensional structural model for a protein of unknown structure can be constructed by using composite parts of related proteins in the same family. Where only the primary amino acid sequence of a target protein is known, the sequence can be compared to the sequences of related proteins with known structures (reference proteins), and a model can be built by incorporating the structural attributes of the reference protein together with the sequence of the target protein.

Sequence homology calculations generally require: the amino acid sequence of the target protein; a high resolution structure for at least one, but preferably more, related reference proteins; and any other related amino acid sequences. The reference proteins include structures which are similar to the target protein, either by sequence, fold, function, or which are polymorphisms of the target protein. The more related protein structures and sequences that are available or determined, the more reliable the technique will be at providing an accurate model.

In constructing a protein model using homology modeling, sequence alignment is performed between the target sequence and any known structures within the protein family. Sequence alignment requires determining the similarity between protein sequences by maximizing the number of matches between the sequences while introducing the minimum number of insertions and deletions. Sequence alignment algorithms are well known in the art, and standard gap penalties (*i.e.*, programs that automatically introduce gaps to maximize alignment and then adjust the percentage of identity by applying penalties for gap number and gap



length) and other parameters can be selected by the skilled artisan. Additionally, the 3-D structures of the known reference proteins, preferably, are aligned to give the best overall fit for the proteins in the family. This provides indication of structurally-conserved regions, such as regions of the proteins that do not contain insertions or deletions, among the reference structures.

Once the sequences are aligned and the structurally-conserved regions are identified, the coordinates of the reference proteins can be used to construct a 3-D model of the target structure. Coordinates from the protein backbone of the reference proteins are then used to construct the backbone framework for the target protein structure. Side chains can be constructed, for example, by using side chain coordinates from the reference proteins, searching from a database to obtain side chain conformations that fit in with the existing structural framework or by generating side chains *ab initio* to establish energetically favorable side chain conformations.

The non-conserved regions of the unknown protein can be constructed, for example, using database searching. A database of known protein structures (*e.g.*, PDB) can be searched to identify variable regions in other proteins that have a high degree of sequence similarity to the target sequence and that fit onto the existing structural framework of the protein model. Algorithms for performing sequence similarity matching and homology model building are well known in the art and are available commercially (available from Molecular Simulations, Inc., Tripos, Inc. and from numerous academic sources).

The variable regions can also be modeled by fitting the target sequence to a peptide backbone generated by varying phi and psi angles (*e.g.*, by calculating Ramachandran or Balasubramanian plots, see, Balasubramanian (1974) "New type of representation for Mapping Chain Folding in Protein Molecules," *Nature* 266:856-857) or Balaji plots, see, U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895) of the amino

acids to give a loop structure that can be integrated into the model structure based on a sterically and energetically reasonable fit (Figure 1).

In a Balasubramanian plot, the peptide is depicted as a series of different vertical lines, each having solid dots and open circles aligned with the corresponding  $\phi$ ,  $\psi$  angle values on the vertical axis, and where each line corresponds to the particular number of the residue having the plotted  $\phi$ ,  $\psi$  angles as indicated on a horizontal axis. In the Balaji plot, the values of the  $\phi$ ,  $\psi$  angles are shown as the base and tip of a vertical wedge (assuming a vertical angular axis), respectively, with a separate wedge being horizontally positioned on the plot as a function of the residue number of the  $\phi$ ,  $\psi$  angles plotted. The Balaji plot replaces the solid dots and open circles of the Balasubramanian Plot with the base of a wedge and the tip of a wedge, respectively; and further replaces the vertical line joining the dots and open circles of the Balasubramanian plot with the body of the wedge.

#### **b. Ab initio generation of 3-D structures**

Alternatively, *ab initio* methods can be used in combination with an existing partial homologous structure to generate unresolved portions of the target structure. Such methods are described, for example, in U.S. Patent Nos. 5,331,573, 5,579,250 and 5,612,895, which as all patents, applications and publications referenced herein, are each incorporated in their entirety. These methods involve: simulating a real-size primary structure of a polypeptide in a solvent box, *i.e.*, an aqueous environment; shrinking the size of the peptide isobarically and isothermally; and expanding the peptide to its real size in selected time periods, while measuring the energy state and coordinates, *i.e.*, the bonds, angles and torsions of the expanding molecule. As the peptide expands to its full size, it assumes a stable tertiary structure. In most cases, due to the manner in which the expansion occurs, this tertiary structure will be either the most probable structure (*i.e.*, it will represent a global minimum for the structure) or one of the most probable structures. The energy

equations used to perform the *ab initio* simulation are based on the potential energy of the simulated molecule as described using molecular mechanics.

Once a model is built, it can be refined using energy minimization, molecular dynamics calculations, or simulated annealing as described herein. The steric and energetic quality of the structural models is then evaluated by analyzing the structural attributes of the model, such as phi and psi angles (*e.g.*, by calculating Ramachandran or Balasubramanian or Balaji plots), or the energetics of the model, such as by calculating energy per residue or strain energy. If the overall quality of the model is not satisfactory, further iterative energy refinement can be performed until the model is considered to be acceptable (*i.e.*,  $e_{av} < 1.5$ , see below).

A preferred method for generating and refining the structural variant models is illustrated in **FIG. 1**. First, at block 100 of FIG. 1, protein sequence information, derived genetic polymorphisms, is obtained from the methods described earlier. At block 102, the protein is assigned to a protein superfamily in order to identify related proteins to be used as templates to construct a 3-D model of the protein. If the superfamily is not known, sequence analysis or structural similarity searches can be performed to identify related proteins for use as templates in homology modeling studies, as described herein, as indicated at block 104.

Once the conserved regions of the model are assembled, *ab initio* loop prediction (Dudek *et al.* (1998) *J. Comp. Chem.* 19:548-573) indicated at 106A or *ab initio* secondary structure generation techniques of block 106B, techniques in which the alignments are adjusted using information on the secondary structure, functional residues, and disulfide bonds as described herein, can be used to complete the model (*e.g.* U.S. Patents Nos. 5,331,573; 5,579,250; and 5,612,895). This model, complete with loops, is then subjected to refinement procedures (block 110) based on molecular mechanics, molecular dynamics, and simulated annealing methods. Energetic refinement of the structure can be

accomplished by performing molecular mechanics calculations using, for example, an ECEPP type forcefield (Dudek *et al.* (1998) *J. Comp. Chem.* 19:548-573) or through molecular dynamics simulations using, for example, a modified AMBER type forcefield (Ramnarayan *et al.* (1990) *J. Chem. Phys.* 92:7057-7076. As known to those of skill in the art a modified AMBER (version 3.3) force field is a fully vectorized version of AMBER (3.0) with coordinate coupling, intra/inter decomposition, and the option to include the polarization energy as part of the total energy (see, *e.g.*, Weiner *et al.* (1986) *J. Comp. Chem.* 7:230-252). If necessary, the 3-D structures can be dynamically refined, for example, by using a simulated annealing protocol (*e.g.*, 100 ps equilibration, 500 ps dynamics, up to 1000°K, 1 fs data collection).

The refinement process step 110 is used to offset problems that may arise when homology models are not built carefully or when they are built using fully automated methods. Problems that may arise include chain breaks (*e.g.* consecutive C $\alpha$  atoms are farther apart than the optimum distance of 3.7 to 3.9 Å); distorted geometry (*e.g.* bond lengths and bond angles are too far from their optimal values); *cis*-peptide bonds (*e.g.*, incorrect isomerization of the peptide backbone in non-proline residues when it is not required); disallowed backbone and side-chain conformations (*e.g.*, dihedral angles do not satisfy the Ramachandran plot (see, Balasubramanian (1974) *Nature* 266:856-857) criteria for a fully favorable protein structure conformation); and misfolded loops (*e.g.* non-homologous loops are generated in unnatural conformations). The refinement procedure 110 removes distortions of covalent geometry by using energetic methods, converts disallowed backbone and side-chain conformations into allowed ones using simulated annealing methods, conserves protein core structure and secondary structural elements built by homology, and rebuilds unnatural loop constructions (Dudek *et al.* (1998) *J. Comp. Chem.* 19:548-573).

For quality control (block 112), the protein structural characteristics, for example, stereochemistry (*e.g.*, phi/psi and side chain angles), energetics (*e.g.*, strain energy), packing profile (*e.g.*, packing factor per residue) and hydrophobic packing are evaluated and required to meet acceptable criteria before the structures are used in further studies or inputted into a structural polymorphism database. Quality control using strain energies entails computing normalized residue energies (NREs) based on the equation:

$$e_i = [E(i,X) - E_{AV}(X)] / E_{SD}(X), \text{ where}$$

$E(i,X)$  is the energy of interactions of amino acid  $X$  in position  $i$  with protein environment and solvent;

$E_{AV}(X)$ ,  $E_{SD}(X)$  is the average residue energies and their standard deviations calculated for 20 amino acids in more than 100 high-quality crystal structures; and

NREs characterize how favorable the interactions of each residue are within the protein environment (Majorov and Abagyan, (1998) *Folding & Design* 3:259).

The average NRE characterizes the overall quality of a protein structure and is defined as:

$$e_{av} = (1/N) \sum_i e_i, \text{ where}$$

$e_{av} \leq 0.5$  denotes high-resolution X-ray crystal structures;

$e_{av} \leq 1.0$  denotes good as NMR and theoretical models; and

$e_{av} \geq 1.5$  denotes structures that require further refinement.

After the quality of structure is determined at block 112, the model is checked at block 114 to determine if it is satisfactory. If the overall quality of the model is not satisfactory, a "No" outcome at block 116, then remedial action is undertaken to fix problems at block 118, including further iterative energy refinement (block 110), and repeated checking (block 114). The refinement and evaluation is repeated until the model is considered to be acceptable, a "Yes" outcome at block 120, whereupon structural and/or physical properties (*e.g.* energetics and phi/psi angles)

are calculated at block 122A and clinical data (if available) is obtained at block 122B. The model is then inputted into a structural polymorphism database at block 124.

FIG. 2 shows an exemplary method for generating structural variant models derived from genetic polymorphisms and using them in structure-based drug design studies. At the block numbered 200, patient data is acquired for a gene that exhibits genetic polymorphisms. Protein sequence information is then derived, at block 202. A check is made for determination of the 3-D structure of the native protein. If the 3-D structure has been determined, a "Yes" outcome at block 206, then a multiple sequence analysis is performed at block 208 to determine the exact amino acid variations for the structure. If the 3-D structure has not been determined, a "No" outcome at block 210, then the structure is determined using physiochemical methods at block 212.

Next, at block 214, the 3-D structural models for all variants are generated. A refinement process is then completed at block 216 for the structural models. As noted above in connection with FIG. 1, the process involves subjecting each model, complete with loops, to refinement procedures based on molecular mechanics, molecular dynamics, and simulated annealing methods. As before, the energetic refinement of the structure can be accomplished by performing molecular mechanics calculations using an ECEPP type forcefield (Dudek *et al.* (1998) *J. Comp. Chem.* 19:548-573), or through molecular dynamics simulations using, for example, a modified AMBER type forcefield (Ramnarayan *et al.* (1990) *J. Chem. Phys.* 92:7057-7076), where a modified AMBER (version 3.3) force field is a fully vectorized version of AMBER (3.0) with coordinate coupling, intra/inter decomposition, and the option to include the polarization energy as part of the total energy (Weiner *et al.* (1986), *J. Comp. Chem.* 7:230-252). If necessary, the 3-D structures can be dynamically refined, for example, by using a simulated annealing protocol

(*e.g.*, 100 ps equilibration, 500 ps dynamics, up to 1000°K, 1 fs data collection).

At block 218, a quality evaluation is performed for all the models. As described in connection with the quality evaluation process in Fig. 1, the evaluation at block 218 involves evaluating the protein structural characteristics, for example, stereochemistry (*e.g.*, phi/psi and side chain angles), energetics (*e.g.*, strain energy), packing profile (*e.g.*, packing factor per residue) and hydrophobic packing, which must meet acceptable criteria before the structures are used in further studies or inputted into a structural polymorphism database.

After the model quality is determined, at block 220 the models are checked to determine if they are satisfactory for further use. If a model is not satisfactory, a "No" outcome at block 222, then the problems are identified and solved with remedial action at block 224. The remedial action may include further iterative energy refinement at block 216 and repeated checks of model quality at block 218. Once the models are satisfactory, a "Yes" outcome at block 226, structure-based drug design methods are applied at block 228 to identify potential new drugs that bind to the structural variant models. The drug design methods are described further below.

FIG. 3 shows another exemplary and alternative method for generating structural variant models derived from genetic polymorphisms and using them in structure-based drug design studies. The process of FIG. 3 is similar to the process of FIG. 2 from the initial process at block 300 of acquiring patient data for a gene that exhibits genetic polymorphisms through the process of obtaining models that are satisfactory (a "Yes" outcome at block 326). Thus, block numbers in FIG. 3 from 300 through 326 that correspond to FIG. 2 blocks numbered from 200 thorough 226 refer to similar operations. Unlike FIG. 2, however, the process illustrated in FIG. 3 then involves docking operations.

At block 328, once the models are determined to be satisfactory, drug molecules are docked with the structural variant models. Next, at block 330, the free energy of binding is evaluated with the potential drugs under study for each structural variant model. At block 332, the total free energy of binding is decomposed, based on the interacting residue in the protein active site. Lastly, at block 334, the free energy of binding is correlated with patient data, if the data is available. Thus, the 3-D structural data is employed in drug design. Details of using such structural data in drug design are described further below.

### c. Crystal structures

The crystal structure of any protein can be determined empirically and the resulting coordinates used as the basis for determining structures of variants. Such structures are often known (see, *e.g.*, Kohlstaedt *et al.* (1992) *Science* 256:1773-1790 for a crystal structure of HIV-1 RT bound to a ligand).

### 3. Use of 3-D structural variant models in drug design

The structural differences in protein structural variants that arise due to genetic polymorphisms can have profound effects on biological activity. Because of the structural differences among the variants, they may have different physical or reactive properties and therefore may exhibit different biological activities. These differences may include, for example, different responses to a given drug, so that a drug which works well in a patient with one particular genetic polymorphism may not work as well in another patient exhibiting a different polymorphism.

The 3-D molecular structures of drug targets derived from genetic polymorphisms can be used in structure-based drug design studies to greatly advance the development of new pharmaceuticals. Relational databases of these 3-D structures that are derived from samplings of genetic polymorphisms over a patient population or a cross-section of the population can be used to design potential drugs in order to optimize effectiveness for the particular population.



The structures and databases described herein can provide information that is useful, for example, in designing a drug that is effective in the greatest percentage of the population. It is desirable that a given drug is effective in the largest percentage of the population, since such a drug is likely to have the greatest clinical utility and thus the greatest commercial value. A drug with superior performance properties is sometimes referred to as a "best in class" drug and is highly prized by pharmaceutical companies since this heralds market leadership and the likelihood of commercial success. The databases and methods described herein can be used to determine 3-D protein structures for drug targets that are associated with particular genetic polymorphisms and to use the structures in drug design studies for design and optimization of candidate drugs that exhibit activity over the broadest patient population.

Genetic polymorphisms may result in target protein structural variants in which drug efficacy correlates with specific populations or subpopulations. In some cases, it might be desirable to target drug design or drug therapy toward a specific patient population, such as a particular race, gender, or age group, affected by a certain disease or condition or toward those having a specific genetic polymorphism. The information derived from comparing the 3-D structural variants arising from different genetic polymorphisms may be useful for understanding why drugs are active or inactive in different subpopulations, or for assisting in developing new drugs to maximize efficacy across specific populations.

**a. Selection of relevant structural variants**

The structural variant models in the structural polymorphism database provided herein can be used to design new drugs or to select a drug therapy that would be appropriate for a patient exhibiting a particular genetic polymorphism. As it may not be possible for a drug to work equally well for all polymorphisms, and thus all patients, representative

structural variants can be selected for use in drug design studies in order to maximize biological activity based on genetic polymorphisms.

In some cases, structural variants are analyzed to determine the common structural features that are conserved through the selected models. These conserved features are used as a basis for drug design. In some cases, the structural variant corresponding to the genetic polymorphism occurring most commonly in a population can be selected for use in identifying drugs that would be effective in the greatest percentage of the population. Optionally, structural variants corresponding to a relevant subpopulation, such as a particular gender, age, race, or other characteristic, can be selected for use in designing drugs that are active in that subpopulation. In other cases, individual structural variant models can be selected for use in designing drugs that are specifically active against one target in one individual arising from a particular genetic polymorphism. Additionally, model structures that represent variants derived from patients that receive a specific treatment regimen or exhibit a particular clinical response (e.g. drug resistance) to a given drug are used as bases for drug design.

The relevant structural variants may be identified using the structural analysis tools described herein, optionally in combination with database and statistical analysis tools that permit a complete analysis and comparison of the molecular structures and properties of the structural variants. The structural variants selected based on the criteria including, but not limited to, those listed above are used in drug design.

#### **b. Drug design**

Once the protein target structural models have been selected, structure-based drug discovery methodologies, for example, computational screening or docking (*e.g.*, DOCK (available from University of Ca, San Francisco; and AUTODOCK available from Scripps Research Institute, La Jolla and others referenced herein or known to those of skill

in the art), can then be used to design biologically-active compounds based on the 3-D structures of the biomolecular receptors.

Using these methods, drug designers can identify and computationally rank various potential clinical drug candidates for maximum efficacy, thus cutting the time and expense associated with drug discovery. The preferred design of drug candidates or the modification of existing drugs is based on the intermolecular interactions between the drug candidate or modified drugs and the selected structural variants predicted by computationally docking drug molecules with the target protein models; energetically refining the docked complexes; determining the binding interactions between the drug or potential new drug candidate molecules and the models by calculating the free energy of binding of the docked complexes and decomposing the total free energy of binding based on interacting residues in the protein active site or sites deemed important for protein activity.

#### **c. Computational docking**

Methods for using the structural variant models to design potential new drugs or to aid in the selection of a drug therapy based on the interactions of selected small molecules with the particular variants are provided. Structure-based drug design experiments, such as computational screening or docking studies, calculation of binding energies or analysis of steric, electrostatic or hydrophobic properties of the resulting structural variant models, can be performed on selected structural variant models to aid in the understanding of observed biological activities or to determine new potential drug candidates to bind to the particular target.

In a typical computational docking protocol, the active site, or sites deemed important for protein activity, of the protein model is defined. A molecular database, such as the Available Chemicals Directory (ACD) or any database of molecules, is screened for molecules that complement the protein model. Solvation parameters are factored in (see, *e.g.*,

Shoichet *et al.* (1999) *PROTEINS: Structure, Function, and Genetics* 34:4-16). In these computational docking studies, drugs or drug candidates are fitted to the structural variant models based on complementary interactions (*e.g.*, steric, hydrophobic, or electrostatic interactions). Methods for performing such studies are well known and software tools for performing the calculations are widely available (M. Lambert, "Docking Conformationally Flexible Molecules into Protein Binding Sites" in *Practical Application of Computer-Aided Drug Design*, Charifson, Ed., Marcel Dekker, NY, pp. 243-303; Kurtz (1992) *Science* 257:1078-1082; Kuntz *et al.* (1982) *J. Mol. Biol.* 161:269-288; Stewart *et al.* (1992) *Med. Chem. Res.* 1:439-443; Shoichet *et al.* (1993) *Science* 259:1445-1450; Shoichet *et al.* (1991) *J. Mol. Biol.* 221:327-346).

New potential drug candidates can be designed by identifying potential small molecule drugs that can bind to a particular structural variant. This is accomplished, for example, by methods including, but are not limited to, methods for electronic screening of small molecule databases as described herein, methods involving modifying the functional groups of existing drugs *in silico*, methods of *de novo* ligand design. Methods for computationally designing drugs are known to those of skill in the art and include, but are not limited to, DOCK (Kuntz *et al.* (1982) "A Geometric Approach to Macromolecule-Ligand Interactions", *J. Mol. Biol.*, 161:269-288; available from University of Ca, San Francisco); and AUTODOCK (see, Goodsell *et al.* (1990) "Automated Docking of Substrates to Proteins by Simulated Annealing", *Proteins: Structure, Function, and Genetics*, 8, pp. 195-202; available from Scripps Research Institute, La Jolla); GRID (Oxford University, Oxford, UK); CAVEAT (UC Berkeley, Ca), LEGEND (Molecular Simulations, Inc., San Diego, CA); LUDI (Molecular Simulations, Inc., San Diego, CA); HOOK (Molecular Simulations, Inc., San Diego, CA); CLIX (CSIRO, Australia); GROW (Upjohn Laboratories, Kalamazoo); others including HINT, LUDI, NEWLEAD, HOOK, PRO-LIGAND and CONCERTS (see, M. Murcko, "An

Introduction to De Novo Ligand Design" in Practical Application of Computer-Aided Drug Design, Charifson, Ed., Marcel Dekker, NY, pp 305-354), methods based on QSAR (quantitative structure-activity relationships, *QSAR and Drug Design: New Developments and Applications*, Fugita, Ed., (1995) Elsevier, pp 3-81; 3D QSAR in Drug Design, Kubinyi, Ed., (1993) Escom, Leiden), and other methods known to those of skill in the art for determining molecules that have optimal binding interactions with a selected target.

The docked complexes, if needed, are further refined energetically to optimize geometries within the binding site and to select the best structure from a set of possible structures, using molecular mechanics, molecular dynamics, and simulated annealing techniques, including those described herein and others that are known to those skilled in the art.

#### **d. Free energy of binding studies**

After the computational docking step, the free energy of binding of the docked complex is calculated, and the total free energy of binding is decomposed based on the interacting residues in the protein active site or sites deemed important for protein activity. Analyses of the binding energies are needed to identify drug candidates. If need or desired, the free energy of binding of different drugs or potential drugs to each structural variant model can be calculated by subtracting the free energy of the non-interacting protein and drug from the free energy of the protein-drug complex. The total free energy of binding is decomposed into its various thermodynamic components, e.g. enthalpic and entropic components, based on the interacting residues in the protein active site in a solvated model to characterize the structural and thermodynamic features in the mode of drug binding and to determine the contribution of the solvent] (see, *e.g.*, Wang *et al.* (1996) *J. Am. Chem. Soc.* 118:995-1001; Wang *et al.* (1995) *J. Mol. Biol.* 253:473-492; Ortiz *et al.* (1995) *J. Med. Chem.* 38:2681-2691, which describes a computational method for deducing QSARs from ligand-macromolecule complexes). Following

the computational drug design protocol described herein, any potential new drugs that are identified can be synthesized in, for example, industry or academia, and subjected to further biological testing, such as *in vitro* studies or pre-clinical and clinical *in vivo* testing.

Based on the predicted intermolecular interactions of the drugs or modified drugs with the structural variant models from binding studies, potential drug candidates that are specific for a protein with a selected polymorphism or that specifically interact with all proteins exhibiting the polymorphism can be identified.

It is also possible to individualize drug design or drug therapy by determining the structural variants associated with a particular patient and then designing or screening drugs or potential drugs to maximize efficacy in that subject or in a subpopulation that exhibits the same genetic polymorphism. The variants may also be used to track polymorphic variations in infectious organisms, such as viruses. For example, the human immunodeficiency viruses (HIVs) reverse transcriptase and protease have served as drug targets (see, Erickson *et al.* (1996) *Ann. Rev. Pharmacol. Toxicol* 36:545-571); their three-dimensional structures are known (see, *e.g.*, Nanni *et al.* (1993) *Perspectives in Drug Discovery and Design* 1:129-150; Kroeger *et al.* (1997) *Protein Eng.* 10:1379-1383). The clinical emergence of drug-resistant variants of these viruses has limited the long-term effectiveness of drugs targeted against these enzymes.

As noted, these enzymatic proteins in order to preserve function must exhibit conserved 3-D structures. The methods herein permit design of drugs specific for the conserved regions of the 3-D structures. They also permit selection of drug regimens based upon the alleles expressed. Hence, methods for designing HIV enzyme-specific drugs are provided. Flow charts illustrating exemplary alternative embodiments using protein 3-D structures derived from genetic polymorphisms in structure-based drug design studies are provided (see, Figs. 2 and 3). In the flow charts

depicted in these figures, the drug design includes structure-based drug design methods (see, Figure 2) and computational docking of drugs with structural variants, evaluation of the binding energy of the docked complexes, and correlation of the binding energy with patient data such as age, gender, race, drug treatment history, and any other pertinent information that is available (see, Figure 3). The data generated by this computer-based method can be stored in a database, such as, for example, in a relational database. The resulting database can be screened using searching tools to select potential drugs and therapeutic agents that bind to or exhibit biological responses towards target proteins.

### **C. Applications of computer-based methods**

As discussed above, the computer-based methods provided herein include some or all of the steps of obtaining one or more, preferably two or more, amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms; generating 3-dimensional (3-D) protein structural variant models from the sequences; and based upon the structures of the 3-D models, designing drug candidates or modifying existing drugs based on the predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants by computationally docking drug molecules with the target protein models; energetically refining the docked complexes; determining the binding interactions between the drug or potential new drug candidate molecules and the models by calculating the free energy of binding of the docked complexes and decomposing the total free energy of binding based on interacting residues in the protein active site or sites deemed important for protein activity. There are numerous applications of these methods, which include structure-based drug design and drug testing; selection of clinically relevant populations for drug testing and other such methods.

## **1. Genetic polymorphisms and structure-based drug design**

As noted above, structure-based drug design is an increasingly useful methodology that has made a great impact in the design of biologically active lead compounds. Drug designers can design and screen potential new drugs via computational methods, such as docking or binding studies, before actually beginning patient testing. The drugs designed by such methods, and also those identified by traditional methods of drug discovery, are then tested in clinical trials. Among those that show efficacy for a particular indication and low toxicity ultimately are approved for use. It is found, however, that not all patients with a particular indication respond uniformly to the drugs. The drug may not be efficacious or side-effects may be pronounced.

The methods provided herein, represent a further advance in the use of rational drug design methods. As described herein, polymorphic variation has an effect upon the 3-D structure of encoded proteins. As a result, drugs interact with variants differently, leading to differential responses in the population as a whole. A new approach to drug design and testing is provided herein. This methods involves identifying polymorphisms and determining 3-D resulting structures, which are then used in methods, including, computational drug design, in the selection of patient populations, in designing treatment protocols and in other applications.

## **2. Drug resistance**

Methods for understanding and overcoming drug resistances by using 3-D protein model structures resulting from multiple genetic polymorphisms or mutations in an infectious agents, such as viruses, bacterial and other pathogenic agents are provided. Also provided are methods that for using this information in drug design studies.

In the case of infectious organisms or other replicating or mutating agents, such as flu, HIV, rhinovirus or biological warfare agents, some polymorphisms or mutations may arise over time which convey resistance



or susceptibility to specific drug therapy, for example, by altering the drug target structure or physical properties so that a specific drug or therapy, such as an antibiotic or vaccine, may no longer be able to bind to or otherwise interact with the target protein to exert its desired biological effect. For certain infectious agents, such as HIV, genetic polymorphisms in certain genes give rise to drug resistance as the virus mutates (see, *e.g.*, Erickson et al. (1996) *Annu Rev. Pharmacol. Toxicol.* 36:545-571).

Where drug resistance that arises from mutations or polymorphisms is observed, the methods described herein can be used to develop new drugs that overcome the resistance. For example, once drug resistance is observed, the structure associated with the resistant polymorphism can be determined and used in further drug design studies to suggest new drugs or modifications to the existing drug that will restore biological activity by targeting different mutants or that will target multiple mutants simultaneously.

The model structures can also be used to correlate drug resistance in infectious diseases with the structural variants derived from genetic polymorphisms. Here, the 3-D structure of the virus or other drug target is determined for the particular variant model against which the drug was effective. When drug resistance arises due to a genetic polymorphism, a model for the structure variant associated with the resistant organism can be generated, and a new drug can be designed or modifications can be made to the existing drug to overcome the resistance.

For example, samples of the mutating organism can be obtained over time and structural models for the resulting proteins can be generated. These models can then be used to design new drug therapies that are active against the mutated organism. Multiple drug resistant structures can be analyzed to obtain an average structure or to identify common structural features in order to design new drugs that have the broadest spectrum of activity against multiple mutations.

Such structural information is useful in designing effective drug therapies to overcome resistance or to develop drugs that are effective over a range of genetic polymorphisms and thus work for the maximum number of patients.

### **3. Identification of conserved structural features or pharmacophores**

If common structural features are observed over a range of protein targets that are derived from genetic polymorphisms, these common features may be used to design a drug that is effective with a variety of genetic polymorphisms and thus many patients. The retention of certain common structural features over a large number of genetic polymorphisms suggests that those features may not be mutable because the conserved structure may be essential to protein function, *e.g.*, to the viability of an infectious organism or virus. Such conserved structural elements are prime targets for structure-based drug design, *e.g.*, anti-infective or antibiotic drug design, and can lead to highly effective therapies.

The common structural features can serve as a basis for structure-based drug design, for example, by serving as a scaffold for building a receptor model into which potential drug candidates can be docked or as a pharmacophore query for screening a library of physical or virtual chemical or biochemical molecules to identify compounds that match the pharmacophore template and, thus, are potential drug candidates.

Analysis of 3-D protein structural variants derived from genetic polymorphisms to identify the common structural features over a large number of structural variants can aid in the design of drugs that are active over a broad range of genetic polymorphisms, such as in a large number of patients or against drug resistant targets.

In comparing sets of related protein structures, such as those with the same biological function or those resulting from genetic polymorphisms, certain parts of the structural framework are often found

to be conserved, while other parts vary among the proteins. Mutations that occur in the conserved regions of the structure can have significant effects biological activity. For example, in viruses, the conserved features can be essential to protein function and, thus, to the viability of the infectious organism or virus. Identifying the conserved structural features over a range of structures often gives insight into which structural features are necessary for biological activity and are therefore non-mutable. By analyzing a number of structural variants derived from genetic polymorphisms that exhibit drug resistance, it is possible to identify or design drugs that interact best with the common structural features in all of the variants. Using these features in structure-based drug design studies leads to the identification of drugs that retain biological activity despite multiple mutations, or polymorphisms, and could help to overcome the problem of drug resistance.

In certain preferred embodiments, new potential drug candidates can be identified using the structural variant models by identifying pharmacophores or conserved features in the protein structural variant models and using this structural information to identify small molecules that would bind to the structural variant models.

Using structural comparison tools described herein, the common structural features that are conserved across a range of structural variant models of a given protein based on different genetic polymorphisms can be identified. To do this, multiple structural variant models are compared, generally by superimposing the coordinates of one variant model onto those of one or more other variants and observing the structural fit. Such functionality is commonly found in molecular graphics or homology modeling packages. Once the optimum fit of structures is performed, then the structural features that are present throughout the structural variant models can be identified and used as the basis for drug interactions in structure-based drug design studies. For example, the pharmacophores or conserved features can be specified as database

queries and a library or database of small molecule structures can be searched to identify new lead compounds to bind to the pharmacophores. Alternatively, other structure-based ligand design strategies can be employed to design lead compounds or to identify modifications to be made to existing drugs to improve biological activity.

#### **4. Identification of compensatory structural changes**

Certain proteins, for example, viral proteins or other infectious organisms, may harbor multiple genetic polymorphisms. Since each genetic polymorphism can give rise to slight changes in structure, some, and over time, many, additional genetic polymorphisms may cause changes in the protein structures that significantly affect biological activity. These structural changes could result in, for example, different dynamical behavior, alteration in enzyme kinetics or differences in substrate recognition, which can significantly alter drug response. For example, a mutation for one drug compound can suppress a mutation to a second drug due to compensatory effects. In these cases, a drug which is predicted to be ineffective for a given patient based upon the single nucleotide correlation may, in fact, be effective as a result of these changes.

Because mutations are so frequent in AIDS and other viruses, few sequences are exactly the same in different patients. Thus, it is difficult or inconclusive to generate multiple mutation sequence correlations for drug resistance. If each patient has a different viral sequence due to a high viral mutation rate, then no sequence correlation is even possible in such cases.

The methods described herein can be used to study the effects of multiple genetic polymorphisms on a resultant protein structure. Multiple mutations are common in AIDS and other viruses, which makes sequence correlation difficult. By observing the structural effects of the mutations on the resulting protein, it is possible to look at the net effect of all structural changes and to consider the overall structure of the protein in

drug design studies. For example, a mutation might occur in the active site, or site of drug action, in a protein. Additionally, there may be related mutations in other parts of the protein structure, which might not be identified from a single point mutation correlation. These related mutations could have an effect on biological activity of the protein. By looking only at the active site, it might be predicted that a drug or potential drug would not bind to the protein. The additional mutation, however, might cause compensatory structural changes in the protein structure that alter its properties in a way that restores biological activity.

By computing 3-D protein structures from gene sequences containing multiple polymorphisms, it is possible to more accurately predict the effect of multiple sequence mutations on protein structure and, thus, to obtain a better correlation between sequence and drug resistance than by considering sequence correlations alone. This information can be useful, for example, in understanding drug resistance and can aid researchers and clinicians in developing new drug therapies to overcome drug resistance.

The structures that are derived based on multiple generic polymorphisms can be used in structure-based drug design studies to provide frameworks, or scaffolds, into which drug or potential drug molecules can be docked. This permits the design of drugs that are active against a wider range of structural variants, thus, in more patients or against a range of drug resistant proteins.

## **5. Clinical Applications**

A knowledge of the repertoire of structural differences arising from genetic polymorphisms across the human population or specific subpopulations can provide insight into the differing biological responses in patients based on their genetic differences. For example, where clinical data are available for patients having particular genetic polymorphisms, this information can be associated with the 3-D protein structural variants

and used to find correlations between polymorphisms and observed drug responses.

The methods provided herein can be used to design drug therapies that bring about favorable clinical responses (or eliminate unfavorable effects) in patients, to identify pharmacological effects of drugs in different patient subpopulations (e.g. age, race, gender) and to simulate clinical trials to increase the probability that the trials will yield optimal results.

Because of the high cost of clinical trials, such studies are generally focused on small patient populations. The structural analysis tools described herein permit the extension of clinical trials to cover patient populations not specifically included in the study. This is accomplished through correlation of the structural variants derived from genetic polymorphisms with clinical responses.

The molecular structures and databases described herein can also find application in the understanding and prediction of clinical or pharmacological drug responses, for example, efficacy, toxicity, dose dependencies or side effects in patients. For example, relational databases containing 3-D protein structural variants can provide a means for managing and using the information to understand and predict clinical responses in patients.

In other embodiments, observed clinical data from patients in a clinical trial can be associated with the structural variant models for each genetic polymorphism exhibited in the clinical subjects, for example, in a structural polymorphism relational database. The correlation between the structural variants and observed clinical effects can then be utilized to predict clinical outcomes in patients that did not participate in the clinical trial. For example, a structural variant model can be generated for a patient based on a genetic polymorphism exhibited in the patient, and the database can be mined to identify structurally similar variants for which clinical results are known. Structural similarity can be determined, for

example, by superimposing the structures and measuring the RMS (root mean squared) differences between the structures or by using pattern matching or motif searching algorithms. The results can be used to predict clinical responses in the patient based on the clinical data associated with the structurally similar variants.

The predicted correlations can also be used to aid in the design of subsequent clinical trials. The follow-on trials can be made more effective through the judicious selection of patients with given genotypes (*i.e.*, those exhibiting the same genetic polymorphisms), as guided by the structurally predicted outcomes. For example, a clinical trial can be designed based on a subpopulation of clinical subjects which exhibit a specific genetic polymorphism (*i.e.* structural variant) to demonstrate the effectiveness of a given therapeutic on a targeted population.

In other embodiments, the methods provided herein can be used in the selection of drug therapies for patients exhibiting a particular genetic polymorphism. This is accomplished by generating the structural variant model associated with the polymorphism, docking drug molecules that might be used to treat the patient into the structural variant model and calculating the binding energies of each drug with the variant. The results of docking or free energy calculations can be correlated to clinical data, for example, patient population (*e.g.*, ethnic background, race, sex, age), treatment regimen, patient response to a particular drug or duration of treatment. The binding energies can be compared, for example, to determine which drug would best bind to the variant in order to identify the drug that could best be used to treat the patient to optimize biological activity.

#### **D. Creation of 3-D Structural Polymorphism Databases**

The above-noted methods all rely upon the use of databases of nucleic acid sequences. Any such database known to those of skill in the art may be employed; numerous such databases are publically available (*e.g.* the Stanford HIV database). The Stanford HIV database is hierarchal

database with information about HIV patients who received or did not receive protease inhibitor treatments, patient-dates, isolates, sequences, hyperlinks to MEDLINE and GenBank abstracts, and art. This database, however, does not contain 3-D protein structures of any proteins including HIV reverse transcriptase (RT) and HIV protease (PR; see, *e.g.*, Shafer *et al.* (1999) *Nucleic Acids Res.* 27:348-352, Shafer *et al.* (1999) *J. Virol* 73:6197-6202, <http://hivdb.stanford.edu/hiv>, Richter (January 20, 1999) "AIDS drugs found to be effective in the world's most common HIV strains).

Databases of sequences and associated information may also be generated as described herein by obtaining samples and sequences from a variety of sources. In all instances, further databases are generated by then calculating 3-D structural models of the encoded proteins or relevant portions, such as active binding sites, thereof, from the nucleic acid sequence information. It is these databases of nucleic acid sequence and/or primary protein sequence and the associated 3-D structure that are provided herein and that are used in the all of the methods, except for the computational phenotyping discussed below, which does not require a database, provided herein. Hence databases containing computationally determined 3-D structures of polymorphic proteins or portions thereof are provided herein. These databases serve as tools in a variety of methods, including those provided herein.

Databases that include 3-D structures for variant proteins encoded by the nucleic acids that contain polymorphisms are provided. These are generated after 3-D structural models are constructed for the protein structural variants, preferably for all of the protein structural variants, representing the genetic polymorphisms, by inputting the atomic coordinates into a structural polymorphism database, preferably a relational database, and optionally with associated structural and/or physical properties (*e.g.*, phi/psi and side-chain angles and energetics), and other data, if available, including, but are not limited to, historical



data, such as parental medical histories, and clinical data. The resulting database is used in structure-based drug design studies and for clinical analyses. Figure 11 is a tabulation of the 3-D coordinates of a representative entry, an HIV protease, that is encoded by the DNA in one of SEQ ID Nos. 3-74 and 77-117, and that is an entry in an exemplary database that includes 3-D structures. Exemplary databases that contain the nucleic acids sequences and structures of all proteins encoded by SEQ ID Nos. 3-117 as well additional nucleic acids are provided herein and are described in the EXAMPLES.

A database is preferably interfaced to a molecular graphics package that includes 3-D visualization and structural analysis tools, to analyze similarities and variations in the protein structural variant models (see, copending U.S. application Serial No. 09/531,995, which is published as International PCT application No. WO 00/57309, and is a continuation-in-part of U.S. application Serial No. 09/272,814, filed March 19, 1999). Briefly, International PCT application No. WO 00/57309 provides a database and interface for access to 3-D molecular structures and associated properties, which can be used to facilitate the design of potential new therapeutics. The interface also provides access to other structure-based drug discovery tools and to other databases, such as databases of chemical structures, including fine chemical or combinatorial libraries, for use in structure-focused high-throughput screening, as well as to a host of public domain databases and bioinformatics sites. The interface also provides access to other structure-based drug discovery tools and to other databases, such as databases of chemical structures, including fine chemical or combinatorial libraries, for use in structure-focused high-throughput screening, as well as to a host of public domain databases and bioinformatics sites. This interface can be modified as needed to adapt for use with a particular database.

A relational database that collects multiple data files relating to the same molecular structure in the same subdirectory and that provides an

interface to access all of the collected files from the same structure using the same user interface program is also provided. The collected files include a variety of information and computer file formats, depending on the type of information to be conveyed to users of the database. In practice, a user communicates over a public network, such as the Internet, or over a controlled network, such as an internet, with a secure file server that controls access to the collected files, and the interface to the collected files is provided by a standard graphical user interface program that is widely available. In this way, a convenient means of searching molecular structure data for characteristics of interest is provided. Data searching, file viewing, and investigation of multiple representations of molecular structures from within a single viewing program can also be performed using the database and interface.

The data files can be those available over a wide network such as the Internet, and a suitable graphical user interface designed or obtained. Such interface is used for viewing the data files is a standard Internet web browser program, such as the web browser products by Netscape Communications, Inc. and Microsoft Corporation that are distributed free of charge. Such browser products readily import and provide views of files having a wide variety of formats that contain alphanumeric, video, and audio data. A security server is preferably located between the user browser program at a network client machine controls access to the database, which is housed at a file server connected to the security server. Before a user gains access to the database, the security server checks authorization for the individual user and then, if appropriate, permits downloading of appropriate data from the database file server. It is contemplated that the databases containing 3-D structures of proteins or portions thereof the exhibit polymorphism will be loaded.

Data for a molecular structure is loaded into the database by specifying the file pathnames for the various data files that contain the different types of data, including the different molecule views. Using a

browser to view the data files permits various helper applications, called plug-ins, to smoothly and transparently accept the different file formats and provide views to the user. The various data files of the database are organized in accordance with the database design when they are loaded into the database and are managed by a relational database management program.

In addition to 3-D protein structures and associated primary sequences, as provided herein, the database can optionally contain associated biological or clinical data, such as drug resistance, side effects, efficacy, pharmacokinetics and other data, that correlate with or can be correlated the structural variants. This information will be used for correlating observed clinical effects to specific structural variants and for predicting clinical responses and outcomes based on a patient's structural variants, *i.e.*, genetic polymorphisms.

Structural analysis tools are preferably integrated with the structural database for comparing and analyzing the resulting protein structural variant models. For example, the molecular graphics software package described in International PCT application No. WO 00/57309, includes structural analysis capability to measure the structural attributes of the model (distances, angles, etc.), to analyze sequences and secondary structures, to study physical properties such as hydrophobicity, electrostatic potential, and active or reactive sites in the protein, as well as to evaluate the quality of the structure (both conformationally and energetically).

Structures can also be compared by aligning them, such as by performing a least squares fitting of the x-, y- and z-coordinates of each of the structural variant models and superimposing the structures or any other alignment method or structural comparison method. For example, the structures of the variants can be clustered, or grouped together, based on structural similarity. This can save time over studying each structural variant independently because, where structures are considered

to be similar enough that they are clustered together (*e.g.*, if their structures can be superimposed within a specified tolerance), then only a representative structure, or perhaps an average structure or scaffold, which is derived as a composite of the individual structural variant models, can be used in further drug design studies.

Tools for database searching can also be included in the software package. These can be used to query the database for structural variant models having similar properties, such as molecular structure or sequence similarity. These tools are used, for example, to mine the database to identify variant models that are structurally similar (*e.g.* to find structures that overlap within a specified tolerance), and thus would be predicted to interact in the same way with potential drugs or exhibit the same clinical response. This information could be useful in understanding the structural or clinical effects of different genetic polymorphisms and could potentially save time and money by extending the results of previously performed clinical or computer-based drug design studies to predict the results of studies on similar structural variants that have not yet been performed.

### **1. Exemplary Databases**

Databases containing data representative of the 3-D structure of structural variants encoded by a selected gene or genes or the 3-D structure of other polymorphic variants are provided. The selected genes can be drug target, such as receptors and genes of infectious agents, such as the HIV protease or reverse transcriptase. Exemplary databases are presented in Example 5 which describes the construction, interface, use and applications of HIV PR and RT databases. These databases may be stored on any suitable medium and used in any suitable computer system. Systems and methods for generating, storing and processing databases are well known.

### **2. Computer systems**

Computer systems for processing the databases and computer systems containing the databases are provided. The processing that maintains the database and performs the methods and procedures using the databases may be performed on multiple computers, or may be performed by a single, integrated computer. For example, the computer through which data is added to the database may be separate from the computer through which the database is sorted or analyzed, or may be integrated with it. Each computer operates under control of a central processor unit (CPU), such as a "Pentium" microprocessor and associated integrated circuit chips, available from Intel Corporation of Santa Clara, California, USA. A computer user can input commands and data from a keyboard and display mouse and can view inputs and computer output at a display. The display is typically a video monitor or flat panel display device. The computer also includes a direct access storage device (DASD), such as a fixed hard disk drive. The memory typically includes volatile semiconductor random access memory (RAM). Each computer preferably includes a program product reader that accepts a program product storage device from which the program product reader can read data (and to which it can optionally write data). The program product reader can include, for example, a disk drive, and the program product storage device can comprise removable storage media such as a magnetic floppy disk, an optical CD-ROM disc, a CD-R disc, a CD-RW disc, or a DVD data disc. If desired, computers can be connected so they can communicate with each other, and with other connected computers, over a network. Each computer can communicate with the other connected computers over the network through a network interface (see, *e.g.*, Examples below) that permits communication over a connection between the network and the computer.

The computer operates under control of programming steps that are temporarily stored in the memory in accordance with conventional computer construction. When the programming steps are executed by

the CPU, the pertinent system components perform their respective functions. Thus, the programming steps implement the functionality of the system as described above. The programming steps can be received from the DASD, through the program product reader, or through the network connection. The storage drive can receive a program product, read programming steps recorded thereon, and transfer the programming steps into the memory for execution by the CPU. As noted above, the program product storage device can include any one of multiple removable media having recorded computer-readable instructions, including magnetic floppy disks and CD-ROM storage discs. Other suitable program product storage devices can include magnetic tape and semiconductor memory chips. In this way, the processing steps necessary for operation can be embodied on a program product.

Alternatively, the program steps can be received into the operating memory over the network. In the network method, the computer receives data including program steps into the memory through the network interface after network communication has been established over the network connection by well known methods that will be understood by those skilled in the art without further explanation.

The computer that implements the client side processing, and the computer that implements the server side processing, or any other computer device of the system, may comprise any conventional computer suitable for implementing the functionality described herein. FIGURE 9 is a block diagram of an exemplary computer device 900 such as might comprise any of the computing devices in the system. Each computer operates under control of a central processor unit (CPU) 902, such as an application specific integrated circuit (ASIC) from a number of vendors, or a "Pentium"-class microprocessor and associated integrated circuit chips, available from Intel Corporation of Santa Clara, California, USA. Commands and data can be input from a user control panel, remote control device, or a keyboard and mouse combination 904 and inputs and output can be viewed

at a display 906. The display is typically a video monitor or flat panel display device.

The computer device 900 may comprise a personal computer or, in the case of a client machine, the computer device may comprise a Web appliance or other suitable Web-enabled device for viewing Web pages. In the case of a personal computer, the device 900 preferably includes a direct access storage device (DASD) 908, such as a fixed hard disk drive (HDD). The memory 910 typically comprises volatile semiconductor random access memory (RAM). If the computer device 900 is a personal computer, it preferably includes a program product reader 912 that accepts a program product storage device 914, from which the program product reader can read data (and to which it can optionally write data). The program product reader can comprise, for example, a disk drive, and the program product storage device can comprise removable storage media such as a floppy disk, an optical CD-ROM disc, a CD-R disc, a CD-RW disc, a DVD disc, or the like. Semiconductor memory devices for data storage and corresponding readers may also be used. The computer device 900 can communicate with the other connected computers over a network 916 (such as the Internet) through a network interface 918 that enables communication over a connection 920 between the network and the computer device.

The CPU 902 operates under control of programming steps that are temporarily stored in the memory 910 of the computer 900. When the programming steps are executed, the pertinent system component performs its functions. Thus, the programming steps implement the functionality of the system illustrated in FIGURE 1. The programming steps can be received from the DASD 908, through the program product 914, or through the network connection 920, or can be incorporated into an ASIC as part of the production process for the computer device. If the computer device includes a storage drive 912, then it can receive a program product, read programming steps recorded thereon, and transfer the programming steps into the memory 910 for execution by the CPU 902. As noted above, the

program product storage device can comprise any one of multiple removable media having recorded computer-readable instructions, including magnetic floppy disks, CD-ROM, and DVD storage discs. Other suitable program product storage devices can include magnetic tape and semiconductor memory chips. In this way, the processing steps necessary for operation in accord with the methods herein can be embodied on a program product.

Alternatively, the program steps can be received into the operating memory 910 over the network 916. In the network method, the computer receives data including program steps into the memory 910 through the network interface 918 after network communication has been established over the network connection 920 by well-known methods that will be understood by those skilled in the art without further explanation. The program steps are then executed by the CPU 902 to implement the processing of the system.

To implement the functionality described herein, it has been found that a suitable computer for performing database server tasks includes a "Pentium" level CPU having at least 128 MB of memory, 30 GB of disk storage, and 256 MB of disk swap space for files. A recommended configuration for computer performance would include, for example, a "Pentium III" processor at 700 MHz or faster, memory of 256 MB or greater, disk storage space of 50 GB or more, and swap space of 500 MB or more. A suitable configuration for performing user tasks as described above includes a "Pentium" level CPU having 128 MB memory, disk space of 240 MB with swap space of 256 MB, and an optional display circuit card supporting OpenGL and having 4 MB of memory. A recommended configuration includes, for example, a "Pentium III" processor at 500 MHz or faster, memory of 256 MB or greater, disk space of 500 MB or more, swap space of 500 MB or more, and an optional display card having 8 MB of memory or more, supporting resolution of 1024 x 768.



In a preferred embodiment, the software used in the computing system described above includes, for the server machine, operating system software such as "Windows NT Server 4.0" from Microsoft Corporation, with Service Pack 5, Version 1280 (10 June 1999) or more recent, with database management server software such as, but are not limited to, "Oracle Server Standard Edition 8.1" from Oracle Corporation. The software used in a preferred embodiment of the user machine includes operating system software such as "Windows NT Workstation 4.0" from Microsoft Corporation, with Service Pack 5, version 1280 (10 June 1999) or more recent, as well as "Oracle Client Standard Edition Version 8.1" or higher. The client machine will also be compliant with the "Java" programming language (Java Runtime Environment 1.2.2). As will be known to those skilled in the art, other configurations may be suitable, depending on the applications being used and the computer performance desired.

#### **E. Computational phenotyping**

Also provided herein is a method designated computational phenotyping. Computational (also referred to herein as *in silico* phenotyping). This refers to the method in which a 3-D protein structure is generated from a given genotype and protein-drug binding analyses *in silico* (computationally) are performed in order to determine whether drug binding does (i.e. sensitive) or does not (i.e. resistant) take place. This type of analysis is contemplated to be performed for an individual patient or subject or groups thereof, such as ethnic groups, gender-based or age-based groups, particular species or groups thereof) to assess or select a drug for treatment of a particular disease or other such use, and is done to assess efficacy of a particular drug on a desired target, where the target exhibits polymorphisms. The following discussion and example, below, is with reference to HIV PR and RT, but it is understood that the methods and applications can be applied to any protein or gene product

that exhibits polymorphic variation, and particularly to gene products that are drug targets.

Among the methods of computational phenotyping, there are three distinct methodologies that are clinically useful for determining either resistance or sensitivity to particular HIV-1 antiviral therapeutics. These are: genotyping, phenotyping, and *virtual* phenotyping. These methodologies are used to optimize the choice of therapeutics during the initiation of therapy, after drug failure, and/or during salvage therapy. Genotyping involves extracting the HIV viral RNA and amplifying all or part of the genes encoding the protease and reverse transcriptase proteins and sequencing them in order to assess the presence of resistance-associated mutations.

In phenotyping, the amplified sequences are instead sub-cloned into expression vectors and then tested for their replicative ability *in vitro* by transfecting them into cultured and/or established cell lines, such as, for example, human T cells, monocytes, macrophage, dendritic cells, Langerhans cells, hematopoietic stem cells, HeLa, XC, Mm5MT, LTL, COS 7, NIH3T3, LTA, MCF-7, or other cells derived from human tissues and cells that which are the principal targets of viral infection in the presence or absence of antiviral drugs (see, *e.g.*, U.S. Patent No. 5,837,464; see, also EP 0852626; EP 1012334; and EP 0877937), *Virtual* phenotyping (ViroLogic, Inc.) is an interpretive service in which the phenotype of a specimen (i.e. of a plant, animal, pathogen, or human) is inferred from the specimen's genotype based upon an extensive correlative database of known genotypes and phenotypes. Such a correlative database must be updated constantly to maintain clinical accuracy.

Similar to *virtual* phenotyping, computational or *in silico* phenotyping infers phenotype based upon specimen genotype. Computational phenotyping is distinct from *virtual* phenotyping in that sensitivity or resistance to drugs is determined directly through protein-drug binding

analysis performed *in silico* and not through correlation with a database of known genotypes and phenotypes. The advantage of computational phenotyping is that new resistance conferring mutations can be discovered rapidly and in "real time" without the need for phenotyping to train the genotype. Moreover, *in silico* phenotypes are not subject to error caused from compensatory mutations which may act synergistically or anti-synergistically with resistance-associated mutations to increase, decrease, or reverse specific drug resistances. Computational phenotyping will generate information that can, for example, be presented in a report that is marketed within the *in vitro* diagnostics industry as an adjunct test/service to help optimize therapy and assist physicians, farmers, academic institutions, government agencies, and industries with specimen treatment. Thus, a computer-based method for predicting clinical responses e.g. drug sensitivity or drug resistance in patients, plants, animals, pathogens, and microorganisms based on genetic polymorphisms is provided.

The genotypes used in the methods are obtained from any source, including, but are not limited to, from a plant, animal, pathogen, or mammal with the most preferred source being a mammal, particularly a human for whom a particular drug treatment is contemplated, and is the genotype of the drug target, such as, as exemplified herein, HIV RT or PR from a particular infected individual. Other exemplary drug targets are proteins, polypeptides, oligopeptides, including, but not limited to, a receptor, enzyme, hormone, and any such compound with which drugs or other ligands interact to bring about a biological response. For exemplification of this method, the protein considered is an enzyme, in particular HIV protease (PR) and reverse transcriptase (RT), which are therapeutic drug targets. Nucleic acid encoding the target from individual sample, such as blood sample or other body fluid sample from a mammal, such as a human patient, is sequenced, and the 3-D structure

thereof determined. The drug of interest is computationally tested to assess whether it interacts with the sample.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

### EXAMPLE 1

#### **BINDING CORRELATIONS OF MUTANT FORMS OF HCV PROTEASE WITH DIFFERENT INHIBITORS**

This example provides the results of a theoretical study of NS3 protease complexes with two known peptide inhibitors (see SEQ ID Nos. 1 and 2; Ingallinella *et al.* ((1998) *Biochemistry* 37:8906-8914).

##### **Introduction**

During HCV replication, the final steps of processing are performed by a virally encoded chymotrypsin-like serine protease NS3. NS3 is an approximately 3000 amino acid protein that contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 4b, 5a and 5b). NS3 is an approximately 68 kDa protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain containing approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family and is a serine protease that is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions responsible for generating four viral proteins during viral replication. This protease is inhibited by N-terminal cleavage products of substrate peptides. The NS3 protease, which is necessary for polypeptide processing and viral replication has been identified, cloned and expressed (see, e.g., U.S. Patent No. 5,712,145).

Active NS3 forms a heterodimer with a polypeptide cofactor NS4A. The crystal structure of NS3 with and without the NS4A cofactor is

known (see, *e.g.*, Love *et al.* (1996) *Cell* 87:331-342; Habuka *et al.* (1997) *Jikken Igaku* 15:2308-2313; Yan *et al.* (1998) *Protein Sci.* 7:837-847, which provides the structure with NS4A).

The NS3 protease is a target for design of antiviral drugs. For example, a series of potent hexapeptide inhibitors of NS3 has been developed by optimization of the product inhibitors (Ingallinella *et al.* (1998) *Biochemistry* 37:8906-8914).

### Analyses

Models of the complexes of NS3 with the two protease inhibitor peptides were obtained by flexible docking of the peptides into the active site of the crystal structure of NS3/4A, followed by evaluation of protein-peptide binding energies. The models were tested by *in situ* modification of the docked ligands. A qualitative agreement between the binding energies and inhibitor IC<sub>50</sub> values obtained from literature was found.

The peptides studied were:

Sequence*	IC <sub>50</sub> , nM	SEQ ID
Ac-Asp <sup>1</sup> -D-Glu <sup>2</sup> -Leu <sup>3</sup> -Ile <sup>4</sup> -Cha <sup>5</sup> -Cys <sup>6</sup> -COO-	15	1
Ac-Asp <sup>1</sup> -L-Glu <sup>2</sup> -Leu <sup>3</sup> -Ile <sup>4</sup> -Cha <sup>5</sup> -Cys <sup>6</sup> -COO-	60	2

\* Cha =  $\beta$ -cyclohexylalanine

In the modeling studies, it was assumed that:

the high-affinity inhibitory peptides 1 and 2 have a similar mode of binding to the active site of NS3;

the minimum binding pharmacophore includes the SH group of Cys<sup>6</sup> and carboxyl groups of Asp<sup>1</sup>, Glu<sup>2</sup> and Cys<sup>6</sup>; and

the side chains of residues 3, 4 and 5 may enhance binding by non-specific hydrophobic interaction with NS3.

### Methods

#### Initial structure of the NS3-peptide complex

The crystal structure of NS3 with a peptide cofactor NS4A was obtained from the arts (Kim *et al.* (1996) *Cell* 87:343) and was used in

the studies with peptide inhibitors. The crystal structure of NS3/NS4A was regularized using molecular mechanics described herein. Initial NS3-NS4-peptide complexes were constructed by placing the peptides into the NS3 binding site expected by structural homology to by other serine proteases:

the C-terminal carboxyl was placed near the oxyanion-stabilizing site (residues 137-139);

the side chain of Cys<sup>6</sup> was inserted into the hydrophobic cavity formed by L135, F154 and A157; and

the  $\epsilon$ -amino group of K136 was placed in contact with the C-terminal carboxyl (see, Kim et al. (1996) Cell 87:343, Steinkuhler *et al.* (1998) *Biochemistry* 37:8899).

#### Monte Carlo simulations

In order to optimize the complexes, Biased Based Probability Monte Carlo (BPMC) simulations (Abagyan et al. (1994) J. Mol. Biol. 235:983) were performed on the NS3-peptide complexes using the ICM program (commercially available from MolSoft, San Diego, CA) with ECEPP/3 force field and atomic solvation energies (Momany *et al.* (1975) J. Phys. Chem. 79:2361, Nemethy *et al.* (1992) J. Phys. Chem. 96:6472, Abagyan *et al.* (1997) Computer Simulations of Biomedical Systems: Theoretical and Experimental Applications, vol. 3, Kluwer Academic Publishers, Dordrecht, The Netherlands, p. 363). The sampling method was BPMC with random change of one variable at a time. A Metropolis acceptance criterion was applied after energy minimization (quasi-Newton, up to 1000 steps). Simulations were performed at a temperature of 1000° K. The peptide translational and rotational degrees of freedom, all peptide torsion angles and  $\chi$  angles of the protein side-chains located within 7.0 Å of any peptide atom were varied during the BPMC simulations.

The energy function used in the MC simulations included:

ECEPP/3 terms for energy *in vacuo* (VDW (van der Waals), H-bond, electrostatic and torsion potentials);

distance dependent electrostatics with  $\epsilon_0 = 4.0$ ; and

surface energy with atomic solvation parameters.

The total energies of the complexes were calculated including contributions from: ECEPP/3 VDW, H-bond, S-S bond and torsion terms; exact-boundary electrostatic energy with  $\epsilon_0 = 8.0$ ; and side-chain entropies. Hydrophobic free energies were estimated as  $sA$ , where  $A$  is accessible surface area and  $s$  is a tension constant of  $0.03 \text{ kcal/mol}\text{\AA}^2$ .

### **Strategy of the flexible Monte Carlo docking**

The simulations proceeded with multiple, relatively short MC runs (2000-5000 generated structures). New docking cycles were started from the lowest-energy or other interesting structures found in previous runs. Structures saved during various MC runs were sorted by total energies and RMSD (root-mean-squared deviation), and compressed into a cumulative conformational stack. Binding energies were calculated for representative structures of each complex thus obtained. This strategy was more efficient than continuous long simulations because the variable torsion angles and distance constraints are defined for an initial structure and do not change during the MC run.

### **Binding energies of the peptide-protein complexes**

For low-energy conformations found after several iterative BMPC cycles, peptide-protein binding energies were estimated using the equation:

$$E_{\text{bind}} = E_0 + E_{\text{compl}} - E_{\text{pept}} - E_{\text{prot}}$$

where  $E_{\text{compl}}$  is the energy of the complex,  $E_{\text{pept}}$  &  $E_{\text{prot}}$  are separate energies of the peptide and protein, respectively, and  $E_0$  is an adjustable constant.

The binding energy function included: exact-boundary electrostatic free energy contributions; side-chain entropy; and surface tension hydrophobic free energy terms. (Zhou and Abagyan (1998) *Folding Design* 3:513, Schapira *et al.* (1999) *J. Mol. Recognition* 12:177). ECEPP/3 hydrogen-bonding terms were included with a weight of 0.5.

## Results

### Models of the NS3-peptide complexes

RMSD between pharmacophore atoms of peptides 1 and 2 were calculated for all pairs of BPMC structures. Two models of the NS3-peptide complexes were selected assuming (1) similar positions of pharmacophore groups of two peptides in the binding site ( $\text{RMSD} \leq 2.0 \text{ \AA}$ ) and (2) low binding energy of the complexes ( $\Delta E_{\text{bind}} < 5.0 \text{ kcal/mol}$ ). Two models of the NS3-peptide complex were selected by visual inspection.

Characteristics of the binding sites for peptide inhibitors in two NS3-peptide complex models are summarized in **Table 1**.

**Table 1**

site	Peptide residue	NS3 residue, group	Type of interaction	Present for Peptide	
				Model 1	Model 2
P1	Cys <sup>6</sup> COO <sup>-</sup>	K136 NH <sub>3</sub> <sup>+</sup> G137 NH S139 OH	H-bond/el. H-bond H-bond	1,2 1,2 1,2	1,2 2 2
	Cys <sup>6</sup> SH	L135, F154, A157	hydroph	1,2	1,2
P2	Cha <sup>5</sup>	H57, R155, A156 A157, V158	hydroph hydroph	1,2 -	- 2
P3	Ile <sup>4</sup>	V132, S133 V158, C159	hydroph hydroph	1,2 -	2 1
P4	Leu <sup>3</sup>	Res. 157 to 160 V132, S133	hydroph hydroph	1,2 -	2 1
P5	Glu <sup>2</sup> COO <sup>-</sup>	R161 guanidine	H-bond/el.	-	1,2
P6	Asp <sup>1</sup> COO <sup>-</sup>	R161 guanidine S133 OH	H-bond/el. H-bond	1,2 -	- 1,2



### Validation of the models: modifications of the protein and ligands in the binding site

In order to validate the proposed models, the K136M mutation and peptide modifications known from SAR (structure-activity relationship) studies were performed in low-energy structures of the NS3-peptide 2 complex.

Positions of the modified ligand and conformations of adjacent protein side chains were adjusted by energy minimization. Distance restraints were applied to keep the ligand near its initial position.

Changes in calculated binding energies upon modifications,  $\Delta E_{\text{bind}}(\text{calc})$ , were compared to the values expected from ratios of inhibitory potencies,  $\Delta E_{\text{bind}}(\text{exp})$ .

$$\Delta E_{\text{bind}}(\text{exp}) = RT \ln(\text{IC}_{50}^{\text{mod}}/\text{IC}_{50}^{\text{o}}),$$

where  $\text{IC}_{50}^{\text{o}}$  and  $\text{IC}_{50}^{\text{mod}}$  are inhibitory potencies of the parent and modified compounds.

The correlation between experimental and calculated changes in binding energy upon ligand modifications in the binding site of NS3 is illustrated in

### FIG. 4.

### Discussion

The two NS3-peptide complex models suggest a common binding pattern for the inhibitor P1 site (Cys<sup>6</sup>-OH) with the carboxyl group hydrogen-bonded to the oxyanion hole residues G137 and S139, and the Cys<sup>6</sup> side chain embedded in a hydrophobic pocket formed by L135, F154 and A157.

This study confirms the possibility of hydrogen bonding between the C-terminal carboxyl and  $\epsilon$ -amino group of K136 suggested by Steinkuhler *et al.* ((1998) *Biochemistry* 37:8899) based on the K136M mutation in NS3. Changes in calculated binding energies upon mutation are consistent with an 8-fold increase in  $K_i$  of an inhibitor with a free

carboxyl group and with the lack of an effect on binding when the peptide is amidated.

The models differ in binding of the negatively charged side chains in positions P5 and P6. The R161 guanidine interacts with a carboxyl group of Asp<sup>1</sup> and Glu<sup>2</sup> in Models 1 and 2, respectively. In Model 2, the Asp<sup>1</sup> carboxyl also interacts with the hydroxyl of S133.

The models are in agreement with SAR data for peptide inhibitors of NS3. Predicted changes in binding energy upon modification of the protein and peptides correlate reasonably well with the changes expected from IC<sub>50</sub> ratios. Standard deviations of  $\Delta E_{\text{bind}}(\text{calc}) - \Delta E_{\text{bind}}(\text{exp})$  were 0.8 and 1.6 kcal/mol for Models 1 and 2, respectively, with correlation coefficients of 0.62. After the largest outlier was removed from each dataset, correlations improved to 0.81 and 0.76, respectively.

### Conclusions

An effective iterative Biased Probability Monte Carlo protocol for the docking of flexible peptide ligands into a flexible protein active site has been developed. Two models of the complexes of HCV NS3 protease with potent peptide inhibitors were proposed based on the docking simulations and on evaluation of protein-ligand binding energies. The models were validated by *in situ* modifications of NS3-peptide complexes and by correlation of binding energies of modified complexes with those expected from experimental IC<sub>50</sub> values. Proposed models can be used for planning further mutagenesis studies of the HCV NS3 protease and the models can be used in the design of non-peptide inhibitors using structure-based drug design methodologies.

### EXAMPLE 2

#### LEAD OPTIMIZATION BY RECEPTOR-BASED FREE ENERGY QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS (QSARS) FOR TNF RECEPTOR ANTAGONIST DISCOVERY

The goal of the modeling studies in this phase was to identify binding modes and complex structures of the compounds that bind to

TNF receptor type I protein in order to guide the design of new compounds. An approach that relies on docking compounds to the receptor, evaluating free energy changes of binding of the docked structures, and comparing the calculated values with experimental inhibition constants  $K_i$  of the compounds was developed. The success of the calculations was assessed by evaluating the consistency of the calculated free energy changes of binding and the experimental  $K_i$ .

The difference in free energy changes of binding between two compounds with inhibition constants  $K_i$  and  $K_i'$  can be calculated as,

$$\Delta\Delta G = -kT \ln K_i'/K_i$$

where  $k$  and  $T$  are Boltzmann's constant and absolute temperature, respectively.

The 13 active compounds were studied. Their potencies, as measured by  $K_i$ , range from 0.1 to 30  $\mu$ M, spanning about 3 kcal/mol in free energy. It was found that the calculated free energy changes of binding are highly consistent with the corresponding experimental values, with correlation coefficient 0.966 and difference less than 0.5 kcal/mol (see Table 2 and Figure 4). The predicted binding modes and complex structures can thus be accepted with confidence.

To modify these compounds, important pharmacophore features on the surface of the receptor that are critical for binding of the compounds were identified. These features include a hydrophobic belt, a hydrophilic belt and 3 hydrogen bond donor sites. A few of potential hydrogen bonding sites, which are not used by the current compounds, were also derived, and can be used for designing more potent binders.

Graphics-guided redesign of the compounds was performed. The free energy calculation was used to predict the binding activity of each design. Fourteen new compounds were thus designed and binding activities were predicted. The chemical structures of the designed molecules, together with the binding modes of the lead compounds, were synthesized and shown to have high affinity for the target. Some of them

exhibit a  $K_i$  in low-nanomolar range. Hence the method provided herein for modification of drugs for binding to calculated 3-D structures of a target protein resulted in redesigned drug candidates with enhanced affinity for the target.

This approach has advantages over the traditional x-ray crystallography method, which include the following:

(1) The binding modes are determined for a group of compounds instead of single compound; analysis of similarity and differences reveals rich information in binding mechanisms.

(2) The predictive power of the free energy calculation is very desirable for redesign of compounds.

(3) The correlation with the biochemical activities assures relevancy of the explored binding modes, while a structure given by x-ray crystallography may not necessarily be one related to the biological functions of the compound.

A comparison of calculated relative free energy changes of binding  $\Delta\Delta A$  and experimental  $\Delta\Delta G$  converted from inhibition constants  $K_i$  (all in kcal/mol) of the compounds (referenced by a code name) is presented in Table 2.

Table 2

Compound	$\Delta\Delta A$	$\Delta\Delta G$
SBI-2030	0	0
SBI-2002	-0.97	-1.25
SBI-2005	-0.72	-1.14
SBI-307	-0.56	-0.08
SBI-2008	-0.53	-0.82
SBI-2006	-0.34	-0.44
SBI-306	-0.07	0.40
SBI-2000	0.29	0.27
SBI-2001	0.72	1.12

Compound	$\Delta\Delta A$	$\Delta\Delta G$
SBI-304	1.55	1.45
SBI-308	1.70	1.78
SBI-305	1.86	1.67
SBI-2048	1.95	1.94

A comparison of calculated *versus* experimental binding free energy changes is given in FIG. 5.

### EXAMPLE 3

#### HIV Protease Models for Drug Studies

Antiviral therapy for AIDS has focused on the discovery and design of inhibitors for two main enzyme targets of the HIV-1: reverse transcriptase (RT) and protease (PR). HIV RT is a heterodimer composed of p51 and p66 subunits. The p51 subunit is composed of the first 450 amino acids encoded by the RT gene and the p66 subunit is composed of all 560 amino acids of the RT gene. RT is responsible for RNA-dependent DNA polymerization, RNaseH activity, and DNA-dependent DNA polymerization.

HIV PR is a homodimer of two identical 99-amino acid chains. HIV PR is an aspartic proteinase that is responsible for the post-translational processing of the viral gag and gag-pol polyprotein gene products, which yields the structural proteins and enzymes of the viral particle (see, *e.g.*, Erickson *et al.* (1996) *Annu. Rev. Pharmacol. Toxicol.* 36:545-571, Bouras *et al.* (1999) *J. Med. Chem.* 42:957-962). Despite several promising new anti-HIV agents, the clinical emergence of drug-resistant variants of HIV limits the long-term effectiveness of these drugs. Genetic analysis of the resistant forms of HIV has identified a number of critical mutations in the RT and PR genes. Moreover, structural analysis of inhibitor-enzyme complexes and mutational modeling studies can lead to a better understanding of how these drug-resistant mutations exert their effects at the structural and functional levels.

### HIV-PR inhibitor computational binding studies

This example provides the results of a computational study on HIV PR. The 3-D protease structure was generated, docked with known viral inhibitors, and analyzed via free energy of binding studies described herein. A quantitative agreement between the calculated and experimental protease-drug binding energies was obtained. Moreover, a series of 3-D HIV PR models were analyzed to identify the invariant regions of the protease. These insights have implications for the design of new drugs and therapeutic strategies to combat AIDS drug resistance.

#### Optimization of 3D structures

Five PR inhibitors approved by the FDA for clinical use were used: saquinavir, nelfinavir, indinavir, amprenavir, and ritonavir (Figure 6). Initial 3-D structures for the wild-type HIV PR complexes with these FDA approved inhibitors were obtained from the Protein Data Bank and were then optimized using Monte Carlo (MC) simulations with an ECEPP/3 force field as described in Example 1. The energy function used in the MC simulations included: ECEPP/3 terms for energy in vacuo (van der Waals, H-bond, electrostatic and torsion potentials); distance dependent dielectrics with  $\epsilon_0 = 4.0$ ; and surface free energy calculated using atomic solvation parameters ((Dudek *et al.* (1998) *J. Computational Chem.* 19:548-573, Wang *et al.* (1995) *J. Mol. Biol.* 253:473-492). Standard ECEPP charges were used for the protein residues. Lys, Arg, Glu, and Asp residues were charged. Charged and protonated states of Asp 125 (chain B) were considered as well. The inhibitors were docked into the active site of the protease, and the protein-drug complexes were energetically refined using the methods described in Example 1. Partial charges for the inhibitors were calculated with the Gasteiger-Marsili method implemented in SYBYL 6.5 (Tripos Assoc., Inc.). Different protonation states were examined for indinavir and amprenavir, but the other inhibitors were assumed to be electroneutral. Water molecules

located within 7.0 Å from a ligand atom in the X-ray structure were retained in the model complex during optimization.

### Calculation of binding energies

For low energy conformations found after several iterative BMPC cycles, protein-drug binding energies were estimated using the equation:

$$E_{\text{bind}} = E_o + E_{\text{compl}} - E_{\text{ligand}} - E_{\text{prot}},$$

where  $E_{\text{compl}}$  is the energy of the complex,  $E_{\text{ligand}}$  &  $E_{\text{prot}}$  are energies of the ligand and protein when separated, and  $E_o$  is an adjustable constant. The binding energies of the protein and ligand were calculated using the following energy function:

$$E = E_{\text{el}} + E_{\text{vw}} + E_{\text{hb}} + E_s,$$

where  $E_{\text{el}}$  is the exact-boundary electrostatic using  $e_o = 8.0$ ,  $E_s$  is the side-chain entropy term, and  $E_{\text{vw}}$  and  $E_{\text{hb}}$  are the ECEPP/3 van der Waals and hydrogen-bonding terms.

After the energies of the wild type PR-inhibitor complexes were calculated, mutation sites were introduced into the optimized X-ray structures or model complexes. The amino acid substitutions were followed by local optimization, using an ECEPP/3 force field, of protein side chains around the mutation sites via the energy minimization of substructures that included the ligand, water molecules within the sphere of radius 7.0 Å around the ligand, and protease residues within the sphere of radius 3-5 Å around the mutated residues. The energy of binding of the mutated complex was calculated based on the equation described herein. The difference in binding energy resulting from mutations (mut) of the wild-type (WT) protease were calculated using the following equation:

$$\Delta E_{\text{bind}}(\text{calculated}) = E_{\text{bind}}(\text{WT}) - E_{\text{bind}}(\text{mut}).$$

This change in binding energy was compared to data from experimental (exptl) studies (Gulnik *et al.* (1995) Biochemistry 35:9282-9287, Klabe *et al.* (1998) Biochemistry 37:8735-8742, Pazhanisami *et al.* (1996) J. Biol. Chem. 271:17979-17985, Jacobsen *et al.* (1995) Virology 206:527-534,

Maschera *et al.* (1996) J. Biol. Chem. 217:33231-33235) based on the equation:

$$\Delta E_{\text{bind}}(\text{exptl}) = RT \ln(K_{\text{mut}}/K_{\text{wt}}).$$

Plots of  $\Delta E_{\text{bind}}(\text{calculated})$  vs.  $\Delta E_{\text{bind}}(\text{exptl})$  were generated, and the results, summarized in Table 3, show a strong correlation between the calculated binding energies and the experimentally determined binding energies for the PR-inhibitor complexes. For example, the correlation coefficient R for PR-ritonavir and PR-amprenavir is 0.9, where R = 1 denotes congruency between the computationally calculated and experimentally determined binding energy data. These correlation data validate the computational protocol and calculations described herein as a method for predicting protein-drug binding or protein-drug resistance (i.e. non-binding). The evaluation of changes in binding energy of protein-drug complexes upon protein sequence variations can be used as a possible descriptor and, thus, can be used to predict the efficacy of drugs on proteins resulting polymorphisms in genes. Moreover, the analysis of the free energy of binding in complexes between the protein models that are produced by the method set forth in this example and drugs that have been designed or modified is a good predictive tool for drug designers.

**TABLE 3**  
Correlation between Experimental and Calculated Binding Energies  
for HIV Protease Inhibitors

HIV PRInhibitor	X-ray Complex ID	No of exptl. data points	Correlation coefficient R	Correlation S.D., kcal/mol
Saquinavir	1HXB	18	0.84	0.68
Indinavir	1HSG	17	0.79	0.80
Ritonavir	1HXW	12	0.90	0.72
Amprenavir	1HPV	15	0.90	0.54
Nelfinavir	1OHR	Insufficient data		

#### Identification of structural invariant regions of HIV Protease

Clinical effectiveness of HIV PR inhibitors is limited by the rapid emergence of drug-resistant mutations. Resistant PR variants first occur



by the mutation of amino acids close to or in and around the drug binding site, which are then accompanied by compensatory mutations of more distant amino acids. The identification of highly conserved, structural invariant regions of a PR would provide new potential targets and thus lead to the development of therapeutics having greater clinical efficacy than those drugs commonly employed to treat HIV.

The protein sequences of HIV protease were obtained from GenBank and from the blood samples of patients using standard isolation and sequencing techniques well known in the arts. The protein sequences were modeled into 3-D structures using the computational protocol described in Example 1. The protease sequences were aligned, and the frequency of mutation, regardless of type, was determined at each amino acid position and plotted in Figure 7, where the frequency of mutation in this set of HIV-1 Protease sequences varied from 0 to 40%. Sequence alignment also revealed how many different types of amino acids could be substituted in any specific residue, yielding the tolerance of each residue to substitutions of different types. The data showing the frequency of mutation of each residue out of PR sequences, the types of mutations, and the distance of the mutating residue from the active site (Asp 28) are shown in FIG. 8. This information, sequences obtained from 10591 different genotypes, was used to identify invariant and/or highly conserved regions of PR and to map these regions to a 3-D structure for the purpose of identifying new potential regions on the protein as targets for therapeutic intervention. These invariant regions include, but are not limited to, residues 1-9, 25-29, 49-52, 78-81, and 94-99, where residue 1 is an aliphatic amino acid, more preferably proline; residue 2 is a hydrophilic amino acid, more preferably glutamine; residue 3 is an aliphatic amino acid, more preferably isoleucine; residue 4 is a hydrophilic amino acid, more preferably threonine; residue 5 is a hydrophobic amino acid, more preferably leucine; residue 6 is an aromatic amino acid, more preferably tryptophan; residue 7 is a hydrophilic amino acid, more

preferably glutamine; residue 8 basic amino acid, more preferably arginine; residue 9 is an aliphatic amino acid, more preferably proline; residue 25 is a hydrophilic amino acid, more preferably aspartic acid; residue 26 is a hydrophilic amino acid, more preferably threonine; residue 27 is an aliphatic amino acid, more preferably glycine; residue 28 is an aliphatic amino acid, more preferably alanine; residue 29 is an acidic amino acid, more preferably aspartic acid; residue 49 is an aliphatic amino acid, more preferably glycine; residue 50 is a hydrophobic amino acid, more preferably isoleucine; residue 51 is an aliphatic amino acid, more preferably glycine; residue 52 is an aliphatic amino acid, more preferably glycine; residue 78 is an aliphatic amino acid, more preferably glycine; residue 79 is an aliphatic amino acid, more preferably proline; residue 80 is a hydrophilic amino acid, more preferably threonine; residue 81 is an aliphatic amino acid, more preferably proline; residue 94 is an aliphatic amino acid, more preferably glycine; residue 95 is a thio-containing amino acid, more preferably cysteine; residue 96 is hydrophilic amino acid, more preferably threonine; residue 97 is hydrophobic amino acid, more preferably leucine; residue 98 is hydrophilic amino acid, more preferably asparagine; and residue 99 is an aromatic amino acid, more preferably phenylalanine. These invariant regions can subsequently be used to assist in the design drugs or therapeutic agents which bind to the invariant regions and disrupt the activity of the protease with greater efficacy than drugs commonly used to treat HIV and where the free energy of binding between said drug or therapeutic agent and the structural invariant region is evaluated as described herein. The methods described in this example can also be applied to HIV RT and to any protein of interest that exhibits polymorphisms.

#### EXAMPLE 4

##### Computational Phenotyping of HIV-1 Protease and Reverse Transcriptase

Computational or *in silico* phenotyping is performed to assess phenotypic properties of a protein. This example demonstrates

application of this method to HIV-1 protease and reverse transcriptase to test whether the efficacy of various protease inhibitors for an HIV patient.

To practice this method 3-D structures of HIV-1 protease and reverse transcriptase based upon the nucleic acid isolated from HIV from a patient are generated. Protein-drug binding analysis *in silico* in order to determine whether drug binding does (i.e. sensitivity) or does not (i.e. resistance) take place.

Sequencing of HIV-1 Protease and Reverse Transcriptase is performed on HIV-1 cDNA following extraction, reverse transcription, and PCR amplification of viral RNA obtained from patient specimens, such as blood samples or other body fluid or tissue samples. Methods for the extraction, reverse transcription, and PCR amplification of viral RNA are well known in the art. For each sequence, a computer-generated 3-D structure of the protein is modeled and then docked with antiviral drugs *in silico* using methods described in Example 1 and elsewhere herein to analyze protein-drug interactions. Antiviral drugs that can be tested include, but are not limited to, saquinavir, indinavir, ritonavir, amprenavir, and nelfinavir for HIV protease; zidovudine, lamivudine, stavudine, zalcitabine, didanosine, abacavir, adefovir, delavirdine, nevirapine, and efavirenz for HIV reverse transcriptase; and any FDA-approved or non-FDA approved antiviral drug. From these protein-drug interaction studies, relative drug resistance or sensitivity is inferred by calculating and evaluating the free energy of binding in low energy conformations of complexes between the variant protease structure and docked antiviral drug or variant reverse transcriptase structure and docked antiviral drug, using the methods described in Examples 1 and 3 and elsewhere herein.

The results of the computational phenotyping procedure can be presented as a patient report that states whether a drug or drugs are sensitive or resistant to the RT or PR obtained from the patient. Such a patient report assists physicians in selecting appropriate drugs for HIV

patients. It also is useful for the *in vitro* diagnostics industry in an adjunct test/service capacity to help optimize antiviral therapy.

### EXAMPLE 5

#### HIV Protease and Reverse Transcriptase Databases

Exemplary databases of the 3-D protein structures of polymorphic variants are described in this example. The HIV PR and RT databases are a comprehensive collection of 3-D polymorphic structural data along with related information, including nucleic acids encoding all or a portion of the protein. These data provide a means to understand differences in the interactions between a drug or drugs and the structural variations of the drug targets.

This example describes the creation, interface for, and use of structural variant databases of HIV protease and reverse transcriptase polymorphic variants.

#### Construction of databases

To implement the RT or HIV database described herein, suitable computer for performing database server tasks includes a "Pentium" level CPU having at least 128 MB of memory, 30 GB of disk storage, and 256 MB of disk swap space for files. A recommended configuration for better computer performance would include, for example, a "Pentium III" processor at 700 MHz or faster, memory of 256 MB or greater, disk storage space of 50 GB or more, and swap space of 500 MB or more. A suitable configuration for performing user tasks as described above includes a "Pentium" level CPU having 128 MB memory, disk space of 240 MB with swap space of 256 MB, and an optional display circuit card supporting OpenGL and having 4 MB of memory. A recommended configuration for better performance would include, for example, a "Pentium III" processor at 500 MHz or faster, memory of 256 MB or greater, disk space of 500 MB or more, swap space of 500 MB or more, and an optional display card having 8 MB of memory or more, supporting resolution of 1024 x 768.

Preferably, the software used in the computing system described above includes, for the server machine, operating system software such as "Windows NT Server 4.0" from Microsoft Corporation, with Service Pack 5, Version 1280 (10 June 1999) or more recent, with database management server software such as "Oracle Server Standard Edition 8.1" from Oracle Corporation, or better. The software used in a preferred embodiment of the user machine includes operating system software such as "Windows NT Workstation 4.0" from Microsoft Corporation, with Service Pack 5, version 1280 (10 June 1999) or more recent, as well as "Oracle Client Standard Edition Version 8.1" or better. The client machine will also be compliant with the "Java" programming language (Java Runtime Environment 1.2.2). As will be known to those skilled in the art, other configurations may be suitable, depending on the applications being used and the computer performance desired.

#### **Database Interface**

The database interface was a Java-based interface with useful features. The database is interfaced to a molecular graphics package that includes 3-D visualization, including wire-frame representations; secondary structure ribbons; and solid surfaces, and structure analysis tools. The database also provides an interface to access all of the collected files from the same 3-D structure. The database interface also provides access to other databases, such as databases of chemical structures and public domain databases such as GenBank and the Protein Data Bank. The OpenGL and C++ module has real-time interaction with the sequence display and sequence analysis modules, such that highlighting residues in one display results in highlighting those same residues in other displays.

The relational database containing the protein information may be structured according to relational objects to facilitate the analysis and computation processes described in the preceding examples. FIG. 10 is a graphical representation of the database objects for the system described

herein. The database is organized by classes, each of which is characterized by data attributes and subclasses for the proteins.

FIG. 10 shows that the database design includes classes comprising Variant and related classes of Sample, Residue, Model, Resistance\_Entry, and Protein. Other classes include Conformation, Residue\_Conformation, Atom, Drug, Family, and Subfamily. These classes store attribute data values and specify class parameters and behaviors to provide the functionality described herein.

For example, FIG. 10 shows that the Variant class stores parameters to specify a variant, including subclasses that specify a Variant\_ID, Sample\_ID, Protein\_ID, Name, and Sequence, where Variant\_ID is the identification number of the variant; Sample\_ID is the identification number of the sample from which HIV PR and RT were obtained; Protein\_ID is the identification number of the protein i.e. PR or RT; Name is the name of the variant distinguishing it from other variants encoded by the same DNA due to ambiguities in the nucleic acid sequence; and Sequence is the nucleotide or amino acid sequence. Similarly, FIG. 10 shows that the Sample class includes subclasses relating to a specific sample and which specify Sample\_ID, Sample\_Date, Sex, Ambiguity\_Number, Distance, Sequence\_Length, Sequence, Clade, and Region, where Sample\_ID is as defined herein; Sample\_Date is the date the sample was obtained; Sex is the gender of the sample donor; Ambiguity\_Number is fraction of ambiguous nucleotide positions; Distance is a normalized number the variation of an amino acid from the master clade; Sequence\_Length is the length of the sequence; Sequence is as defined herein; Clade is the master sequence; and Region is the geographic location from which the sample was obtained. The Model class includes subclasses comprising Model\_ID, Model\_Name, Variant\_ID, and Drug\_ID, where Model\_ID is the identification number of the 3-D protein model; Model\_Name is the name of the 3-D protein model; Variant\_ID is as defined herein; and Drug\_ID is the identification number

2025 RELEASE UNDER E.O. 14176

of the drug i.e. antiviral drug. The atom class includes the subclasses comprising Atom\_Name, Residue\_Conformation\_ID, X\_Coordinate, Y\_Coordinate, and Z\_Coordinate, where Atom\_Name is the name of atom in the 3-D protein structure; Residue\_Conformation\_ID is the identification number of the amino acid conformation in a 3-D structure; and X\_Coordinate, Y\_Coordinate, and Z\_Coordinate are the coordinates of the 3-D protein structure. The conformation class includes the subclasses comprising Conformation\_ID, Model\_ID, and Refinement\_Level, where Conformation\_ID is the identification number of a conformation of a 3-D structure; Model\_ID is as defined herein, and Refinement\_Level is the number of times the conformation was refined energetically. The drug class includes the subclasses comprising Drug\_ID, Profile, Symbol, Name1, Name2, Company, and URL, where Drug\_ID is as defined herein; Symbol is the FDA symbol for the drug; Name1 is the name of the drug, Name2 is an alternative name of the drug; Company is the company that makes the drug; and URL is the website address of the company that makes the drug. The residue\_conformation class includes the subclasses comprising Residue\_Conformation\_ID, Conformation\_ID, and Residue\_ID, where Residue\_Conformation\_ID is as defined herein; Conformation\_ID is as defined herein; and Residue\_ID is the identification number of the amino acid. The Resistance\_Entry class includes the subclasses comprising Resistance\_Entry\_ID, Profile, Protein\_ID, Residual\_Number, Amino\_Acid, Weight, and Maximum\_Weight, where Resistance\_Entry\_ID is; Protein\_ID is as defined herein, Amino\_Acid is the amino acid. The Family class includes the subclasses comprising Family\_ID and Family\_Name, where Family\_ID is the identification number of the protein family and Family\_Name is the name of the protein family. The SubFamily class includes the subclasses comprising SubFamily\_ID, SubFamily\_Name, and Family\_ID, where SubFamily\_ID is the identification number of the protein subfamily, SubFamily\_Name is the name of the protein subfamily, and Family\_ID is as defined herein. The Protein class includes the

subclasses comprising Protein\_ID, Protein\_Name, Species, Multiple\_Domain, Multiple\_Chain, and Wild\_Type, where Protein\_ID is as defined herein, Protein\_Name is the name of the protein i.e. RT or PR; Species is the species of the source of the protein i.e. humans; Multiple\_Domain is the domain of the protein i.e p66 or p51 in the case of RT; Multiple\_Chain is the a or b chain in the dimers of RT and PR; and Wild\_Type is the wild-type protein sequence for RT and PR. The residue class includes the subclasses comprising Residue\_ID, Variant\_ID, Chain, Residue\_Number, Insertion\_Code, and Residue\_Code, where Residue\_ID is the identification number of the amino acid, Variant\_ID is as defined herein, Chain, Residue\_Number is the numbering of an amino acid in a protein sequence, Insertion\_Code is the identification number if different insertions occur in the amino acid sequence, and Residue\_Code is the single letter or 3-letter code of an amino acid. Those skilled in the art will understand the database design exemplified in FIG. 10. It should be understood that other classes or parameters may be included, as selected by those skilled in the art, for the desired database design.

#### **Database Content**

The databases contain information on the variants of HIV PR and RT present in patient populations. The master amino acid sequence, nucleic acid sequence, and 3-D structure are obtained from GenBank; an exemplary master sequence is set forth in SEQ ID No. 118. Nucleotide sequences exhibiting polymorphisms and the corresponding structural variant protein sequences are determined by isolating nucleic from viruses and viral nucleic acid obtained from the blood samples of patients throughout the US, as well as from other countries, using sequencing methods well known in the art. The sequences were inputted into the RT and PR databases. Exemplary of the nucleotide sequences and the encoded amino acids for HIV RT and PR in this data base are set forth in SEQ ID NOS. 3 to 117, where r is g or a; y is t/u or c; m is a or c; k is g or t/u; s is g or c; w is a or t/u; b is g or c or t/u; d is a or g or t/u; h is a



or c or t/u; v is a or g or c; and n is a or g or c or t/u or unknown or other. The amino acid sequences of the wild type and structural variants are used to create 3-D protein structures which are deposited into the databases.

### 1. 3-D Protein Models

The structure of the wild-type or master sequence model of PR and RT were obtained from the crystal structures found in PDB. The initial structure was refined energetically using BPMC with an ECEPP force field as described in Example 1. The quality of the model was assessed by calculating Normalized Residue Energies (NREs), where models with  $e_{av} \geq 1.5$  require further energetic refinement; and models with  $e_{av} < 1.5$  were deposited into the database as described herein. The 3-D protein structures of the variant sequences were generated by comparing these structures to the master sequence (see, *e.g.*, SEQ ID No. 118; *i.e.*, homology modeling) and energetically refining the models *ab initio*, using the same force field and BPMC procedure as the master sequence and applying the same quality control standard as described herein. Figure 11 is a tabulation of the 3-D coordinates of an exemplary HIV PR entry in a database that includes 3-D structures. For US purposes and where permitted, Tables 4 and 5 are provided electronically on CD ROM. These Tables house the coordinates that represent the 3-D protein structures of proteins encoded by the nucleic acids set forth in SEQ. ID. NOS. 3-117. It will be noted that these sequences encode a full length PR and about 200 nucleotides the p51 subunit, which is the subunit of interest herein. To construct the full-length 3-D structure, the 3-D structure of each encoded portion of the p51 subunit was generated and then combined with the structure of the master sequence to produce a full-length structure.

These 3-D structures in the database can be selected and exported into computational docking programs for analyzing protein-drug interactions on known drugs, new drugs or modified drugs. The database

can be mined to find protein models that correspond to patients with a particular genetic polymorphism, patients with the most commonly occurring polymorphism, to a relevant patient subpopulation (*e.g.*, gender, age, race, or other characteristic), to patients receiving a specific treatment regimen, to patients exhibiting a particular clinical response, to structural invariants, or to other relevant criteria.

Drugs can be docked into the active sites of PR and RT and subsequently energetically refined using an ECEPP force field and BPMC as described in Example 1. The quality control is that the protein-drug complex represents a low energy conformation, which may take several iterative BMPC cycles. Then, the binding energies of the protein-drug complexes can be estimated using the methods of Example 1. Drug designers can modify the structures of drugs or design new drugs, using methods well known in the arts, to maximize the drug binding to the models generated by this database.

## **2. Other Data**

Each PR or RT nucleotide sequence in the database has associated with it an identification number, the nucleotide sequence length, the translated amino acid sequence (or sequences in cases of ambiguous nucleotide positions), a 3-D structure for each amino acid sequence (from which a number of structurally related values are calculated), the genotyping date, the gender of the patient, the geographical location from which the sample was sent, the clade of the sequence, the fraction of ambiguous nucleotide positions, drug information, and other clinical information.

### **Database Usage**

A query menu allows the user to retrieve data based on the various fields: sample ID, residue number (with or without specific amino acid mutation), date gender, geographic location, distance from the master sequence, and other useful queries. The set of sequences that satisfies the user's query are brought up in a sequence display module, which

have variations from the master sequence indicated initially, although the sequences can be highlighted according to predicted resistance. This subset of sequences can be subjected to further analyses. For example, a histogram summarizing the number of mutations at each position in the subset can be generated. The 3-D structures for any of the variants in the database can be displayed and analyzed in the structure visualization module, allowing the user to compare the similarities and differences between 3-D structures by superimposing the 3-D structures. The user can also export these structures into programs for protein-binding studies as described herein. Thus, by mining the databases, a user will access 3-D structures and clinical and sample information that can be used in and correlated with protein-drug binding studies of HIV PR and RT.

#### **Database Applications**

The HIV PR and RT databases have many applications. The applications include, but are not limited to, any application and method provided herein, such as databases that assist in de novo drug design and drug binding calculations. In particular, the database can be used in the design of 2nd and 3rd generation drugs to combat potential resistance to HIV therapy, and it can be used in the design of drugs that will impact a broad spectrum of the infected population. The databases provide the ability to design drugs that focus on the most highly conserved regions of a drug target and drugs that will avoid resistance to mutation. The database could be used to rank drug candidates by likely efficacy within a given subpopulation of patients (e.g. age, race, gender) in pre-clinical trials and to predict the most effective drug regimen to give a patient, and for designing clinical trials.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

**CLAIMS**

1. A computer-based method of drug design based on genetic polymorphisms, comprising:

obtaining more than one amino acid sequence of target proteins that are the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

generating 3-dimensional (3-D) protein structural variant models from the sequences; and

based upon the structures of the 3-D models, designing drug candidates, modifying existing drugs, identifying potential drug candidates or identifying modifications of existing drugs based on predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants.

2. The method of claim 1, wherein the structure-based drug design method comprises:

computationally docking the drug candidate or modified drug molecules with the target protein structural variant models;

energetically refining the docked complexes;

determining the binding interactions between the drug candidate or modified drug molecules and the structural variants; and

designing and identifying drugs or modifications to existing drugs based on the binding interactions.

3. The method of claim 2 wherein the binding interactions are determined by:

calculating the free energy of binding between the protein structural variant model and the docked molecule; and

decomposing the total free energy of binding based on the interacting residues in the protein active site.

4. The method of claim 1 wherein:

after the protein structural variant models derived from a particular genetic polymorphism are generated, selected model structures are

analyzed to determine common structural features that are conserved throughout the selected models, wherein

the conserved structural features are used as a basis for structure-based drug design studies.

5. The method of claim 4, wherein the conserved structural features are stretches of non-contiguous residues, wherein each stretch contains at least two amino acids.

6. The method of claim 5, wherein the protein is human immunodeficiency virus protease.

7. The method of claim 6, wherein the conserved residues comprise residues 1-9, 25-29, 49-52, 78-81 and 94-99; and wherein:

residue 1 is an aliphatic amino acid; residue 2 is a hydrophilic amino acid; residue 3 is an aliphatic amino acid; residue 4 is a hydrophilic amino acid; residue 5 is a hydrophobic amino acid; residue 6 is an aromatic amino acid; residue 7 is a hydrophilic amino acid; residue 8 is a basic amino acid; residue 9 is an aliphatic amino acid; residue 25 is an acidic amino acid; residue 26 is a hydrophobic amino acid; residue 27 is an aliphatic amino acid; residue 28 is an aliphatic amino acid; residue 29 is an acidic amino acid; residue 49 is an aliphatic amino acid; residue 50 is a hydrophobic amino acid; residue 51 is an aliphatic amino acid; residue 52 is an aliphatic amino acid; residue 78 is an aliphatic amino acid; residue 79 is an aliphatic amino acid; residue 80 is a hydrophilic amino acid; residue 81 is an aliphatic amino acid; residue 94 is an aliphatic amino acid; residue 95 is a thio-containing amino acid; residue 96 is a hydrophilic amino acid; residue 97 is hydrophobic amino acid; residue 98 is hydrophilic amino acid; and residue 99 is an aromatic amino acid.

8. The method of claim 6, wherein the conserved residues comprise residues 1-9, 25-29, 49-52, 78-81 and 94-99; and wherein:

residue 1 is proline; residue 2 is glutamine; residue 3 is isoleucine; residue 4 is threonine; residue 5 is leucine; residue 6 is tryptophan; residue 7 is glutamine; residue 8 is arginine; residue 9 is proline; residue 25 is aspartic acid; residue 26 is threonine; residue 27 is glycine; residue 28 is alanine; residue 29 is aspartic acid; residue 49 is glycine; residue 50 is isoleucine; residue 51 is glycine; residue 52 is glycine; residue 78 is glycine; residue 79 is proline; residue 80 is threonine; residue 81 is proline; residue 94 is glycine; residue 95 is cysteine; residue 96 is threonine; residue 97 is leucine; residue 98 is asparagine; and residue 99 is phenylalanine.

9. The method of claim 6, wherein the HIV protease has the sequence of amino acids set forth in any of SEQ ID Nos. 3-74 and 77-117.

10. The method of claim 9, wherein the residues comprise residues 1-9, 25-29, 49-52, 78-81 and 94-99.

10. The method of claim 1, wherein the selected model structures represent the structural variants resulting from the most commonly occurring genetic polymorphisms.

11. The method of claim 1, wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a selected patient subpopulation.

12. The method of claim 1 wherein the structural variant models are stored in a relational database, comprising:

3-D molecular coordinates for the structural variants;  
a molecular graphics interface for 3-D molecular structure visualization; computer functionality for protein sequence and structural analyses; and  
database searching tools.

13. The method of claim 12, wherein the database further comprises one or more of observed clinical data associated with the genetic polymorphisms, subject medical history and subject history.

14. The method of claim 1, wherein:

after generating the 3-D protein structural variant models,  
the method comprises:

computationally docking drug molecules with the target  
protein models; and

energetically refining the docked complexes; and

wherein the candidate drugs are specific for a protein with a  
selected polymorphism or specifically interact with all proteins exhibiting a  
polymorphism.

15. The method of claim 14, wherein the structure-based drug  
design method comprises:

computationally docking drug or potential new drug candidate  
molecules with the target protein structural variant models;

energetically refining the docked complexes;

determining the binding interactions between the drug or potential  
new drug candidate molecules and the structural variants; and

designing potential new drugs or modifications to existing drugs  
based on the binding interactions.

16. The method of claim 15, wherein the binding interactions are  
determined by:

calculating the free energy of binding between the protein  
structural variant model and the docked molecule; and

decomposing the total free energy of binding based on the  
interacting residues in the protein active site.

17. The method of claim 14, wherein:

after the protein structural variant models derived from a particular  
genetic polymorphism are generated, selected model structures are  
analyzed to determine common structural features that are conserved  
throughout the selected models; and

the conserved structural features are used as a basis for structure-  
based drug design studies.

18. The method of claim 17, wherein the selected model structures represent the structural variants resulting from the most commonly occurring genetic polymorphisms.

19. The method of claim 17, wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a specific patient subpopulation.

20. The method of claim 12, wherein the selected model structures represent structural variants derived from patients the receive a specific treatment regimen.

21. The method of claim 12, wherein the selected model structures represent structural variants derived from patients that exhibit a particular clinical responses to a given drug.

22. The method of claim 12, wherein the selected model structures represent structural variants derived based on the duration of a particular drug treatment.

23. The method of claim 12, wherein the structural variant models are stored in a relational database, comprising:

3-D molecular coordinates for the structural variants;  
a molecular graphics interface for 3-D molecular structure visualization; and  
functionality for protein sequence and structural analysis; and  
database searching tools.

24. The method of claim 12, wherein the database further comprises observed clinical data associated with the genetic polymorphisms, subject medical history and subject history.

25. A computer-based method of selecting drug therapies for patients based on genetic polymorphisms, comprising:

obtaining amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;



generating 3-D protein structural variant models from the sequences;

computationally docking drug molecules with the target protein models;

energetically refining the docked complexes;

determining the binding interactions between the drug or potential new drug candidate molecules and the models; and

selecting drug therapies based on the drug or drugs that have the most favorable binding interactions with the structural variant models.

26. The method of claim 25, wherein the binding interactions are determined by:

calculating the free energy of binding between the protein structural variant and the docked drug molecule; and

decomposing the total free energy of binding based on the interacting residues in the protein active site.

27. The method of claim 1, further after generating the 3-D structural variant models, exporting some or all of them models into a program that computationally docks the models with test compounds to assess intermolecular interactions.

28. A computer-based method for predicting clinical responses in patients based on genetic polymorphisms, comprising:

obtaining one or more amino acid sequences for a target protein that is the product of a gene exhibiting genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

building a relational database of protein structural variants derived based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the patients, wherein the database comprises:

3-D molecular coordinates for the structural variant models;

a molecular graphics interface for 3-D molecular structure visualization;

computer functionality for protein sequence and structural analysis;

database searching tools; and

observed clinical data associated with the genetic polymorphisms, subject medical history and subject history associated with the genetic polymorphisms;

obtaining a target protein structural variant based on the same gene associated with a polymorphism in a patient;

generating a 3-D protein model based on the subject's gene sequence;

screening/comparing the 3-D model derived from the subject to the structures contained in the database by:

identifying structures in the database that are similar to the model derived from the subject; and

predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

29. A computer-based method for designing therapeutic agents that are active against biological targets that have become drug resistant due to genetic mutations, comprising:

obtaining a first 3-D protein structural variant model of a target protein against which a given drug has biological activity;

generating a second 3-D protein structural variant model of the target in which genetic mutations have occurred and against which the same drug is no longer biologically active;

comparing the structures of the first and second model to identify structural differences; and

performing structure-based drug design calculations in order to identify new drugs or modifications to the existing drug to bring about biological activity against the second model.

30. A computer-based method for identifying compensatory mutations in a target protein, comprising:

obtaining the amino acid sequence of a target protein containing multiple amino acid mutations that is expressed in a patient, wherein the structure of a form of the target protein that responds to a particular drug, including the active site, has been structurally characterized;

generating a 3-D structural model of the mutated protein;

comparing the structure of the mutated protein with the form of the protein that responds to the drug to identify structural differences and/or similarities arising from the mutations;

comparing the biological activities of the drug against both the mutated protein and the form of the protein that responds to the drug to determine the effects of the mutations on drug response; and

identifying the mutations in the protein that affect biological activity based on the comparisons.

31. A method for creating a 3-D structural polymorphism relational database, comprising:

obtaining one or more amino acid sequences of a target protein that is the product of a gene exhibiting a genetic polymorphism, wherein sequences represent different genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

energetically refining the models;

evaluating the quality of the models;

optionally obtaining associated clinical properties or data; and

inputting the model and any associated properties and/or data into a relational database.

32. The method of claim 31, wherein after energetically refining the models, the models are further refined.

33. The method of claim 31, wherein the database comprises amino sequences of two or more polymorphic variants.

34. The method of claim 31, wherein the database comprises amino sequences of ten or more polymorphic variants .

35. The method of claim 31, wherein the database comprises amino sequences of about 100 or more polymorphic variants .

36. The method of claim 31, wherein the database comprises amino sequences of about 1000 or more polymorphic variants .

37. The method of claim 31, wherein the database comprises amino sequences of more than 8000 polymorphic variants.

38. A database created by the method of claim 31.

39. The database of claim 38, comprising variant 3-dimensional structures of a selected target.

40. The database of claim 38 that comprises structures of proteases or polymerases.

41. The database of claim 38, wherein the proteases are viral proteases or polymerases.

42. The database of claim 38, wherein the viral proteases are human immunodeficiency virus proteases and the polymerase is a viral reverse transcriptase.

43. The method of claim 31, wherein quality is assessed by computing the normalized residue energies such that if  $e_{av}$  is  $\geq 1.5$  a model is further refined until  $e_{av}$  is  $< 1.5$ ; if  $e_{av}$  is  $< 1.5$  a model is deposited into the database.

44. The method of claim 1, wherein the target is an enzyme.

45. The method of claim 44, wherein the enzyme is a protease or polymerase.

46. The method of claim 45, wherein the polymerase is a reverse transcriptase.

47. The method of claim 44, wherein the target is a protein expressed by an infectious agent.

48. The method of claim 44, wherein the target is enzyme expressed by a an infectious agent.

49. The method of claim 48, wherein the agent is a human immunodeficiency virus (HIV).

50. A computer system, comprising a database containing data representative of the three dimensional structure of polymorphic variants of a drug target.

51. The system of claim 50, wherein the target is a cell surface receptor or an enzyme.

52. The system of claim 50, wherein the enzyme is a protease or a polymerase.

53. A database, comprising:  
sequences of nucleotides encoding a protein or portions thereof, wherein proteins comprise polymorphic variants; and the portions encode a domain of the protein that comprises a site in the protein that binds to a drug candidates; and

the coordinates of 3-dimensional (3-D) structures of the encoded proteins or portions thereof.

54. The database of claim 53 that is a relational database.

55. The database of claim 53 that comprises at least 2 polymorphic variants and the corresponding 3-D structures.

56. The database of claim 55 that comprises at more than 10, more than 100, more than 1000, more than 8000, or more than 10,000 polymorphic variants and the corresponding 3-D structures.

57. The database of claim 53, wherein the protein is a receptor or enzyme from a eukaryotic or prokaryotic organism.

58. The database of claim 53, wherein the organism is a pathogen or a mammal.

59. The database of claim 53, wherein the organism is a pathogen is a virus or bacterium and the mammal is a human.

60. The database of claim 53, wherein the protein is a protease or a reverse transcriptase.

61. A database, comprising the sequences of nucleotides set forth in SEQ ID Nos. 3-117 that encode HIV protease or the portion of HIV reverse transcriptase set forth in each SEQ ID.

62. The database of claim 53, further comprising 3-D structural coordinates for a protein or portion thereof comprising sequences of amino acids encoded by each of SEQ ID Nos. 3-117.

63. The database of claim 54, wherein the protein is HIV protease.

64. The database of claim 54, wherein the protein is HIV reverse transcriptase.

65. The method of claim 1, wherein the target protein is a eukaryotic or prokaryotic protein.

66. The method of claim 1, wherein the target protein is an animal protein, a plant protein or a protein from a pathogen.

PROTEIN SEQUENCES

### ABSTRACT OF THE DISCLOSURE

Provided herein are computer-based methods for generating and using three-dimensional (3-D) structural models of target molecules and databases containing the models. The targets can be protein structural variants derived from genes containing polymorphisms. The models are generated using molecular modeling techniques and are used in structure-based drug design studies for identifying drugs that bind to particular structural variants in structure-based drug design studies, for designing allele-specific drugs and population-specific drugs and for predicting clinical responses in patients. Computer-based methods for predicting drug resistance or sensitivity via computational phenotyping are also provided. Databases containing protein structural variant models are also provided.

NOOT 7 2266266

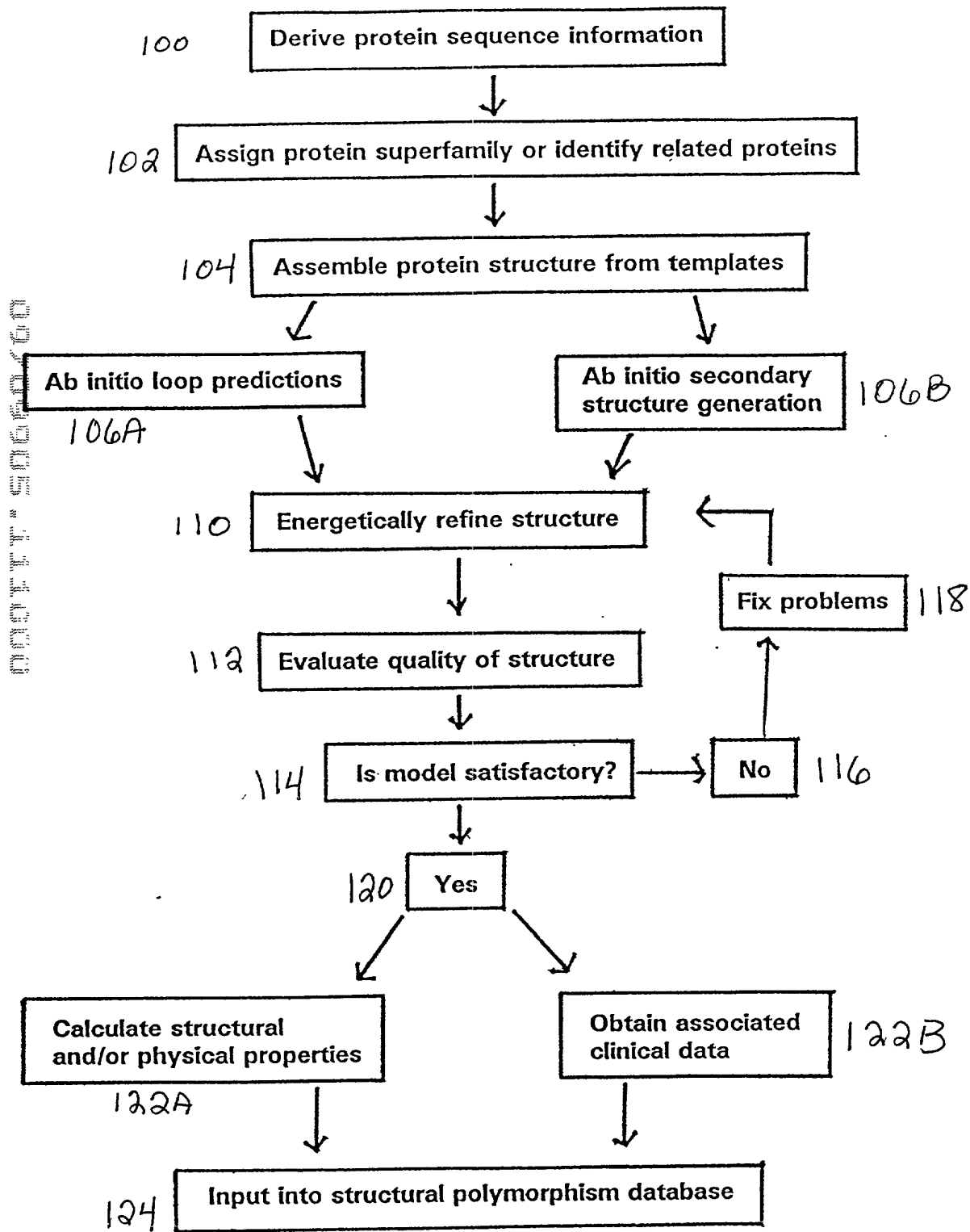


FIG. 1



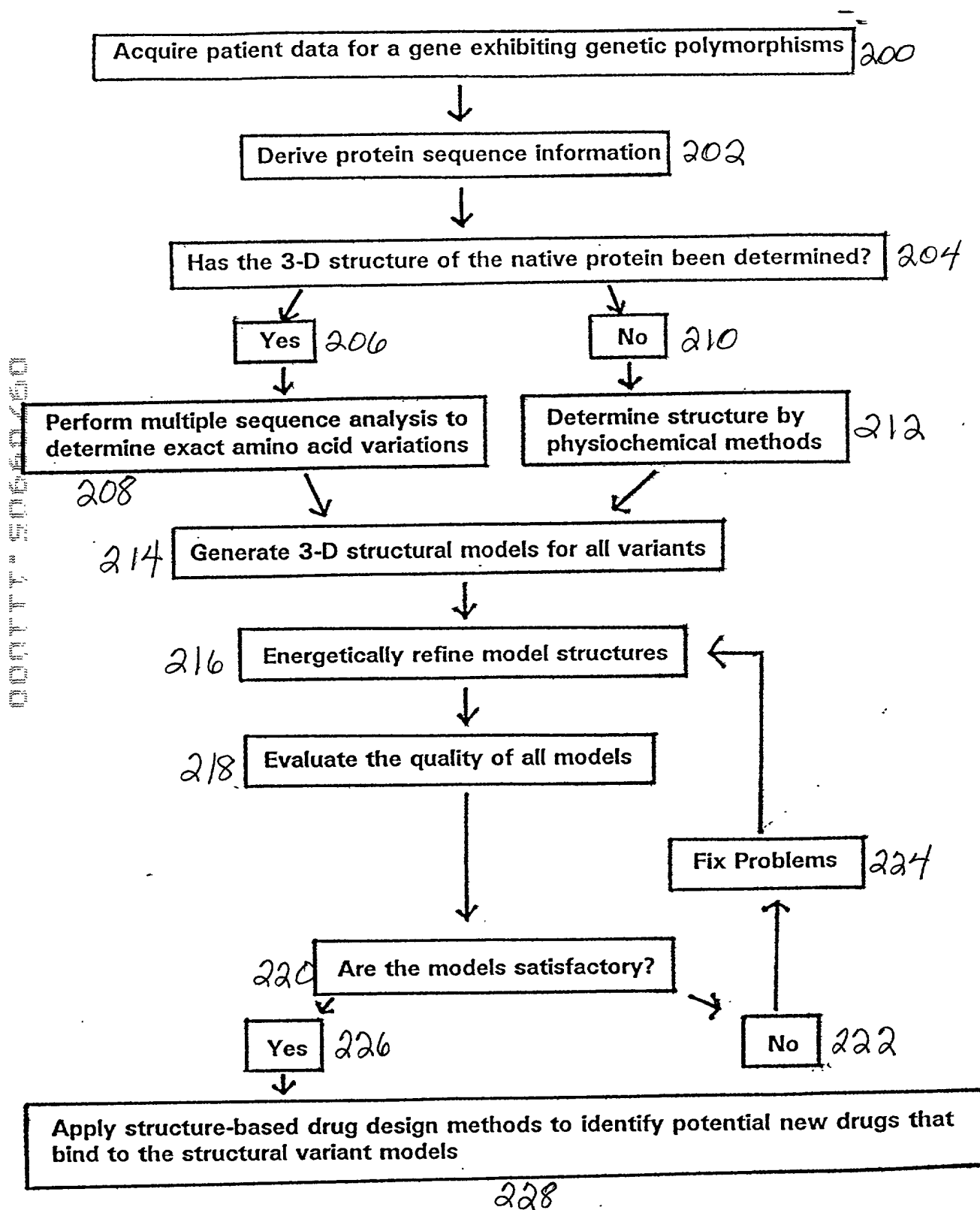


FIG. 2

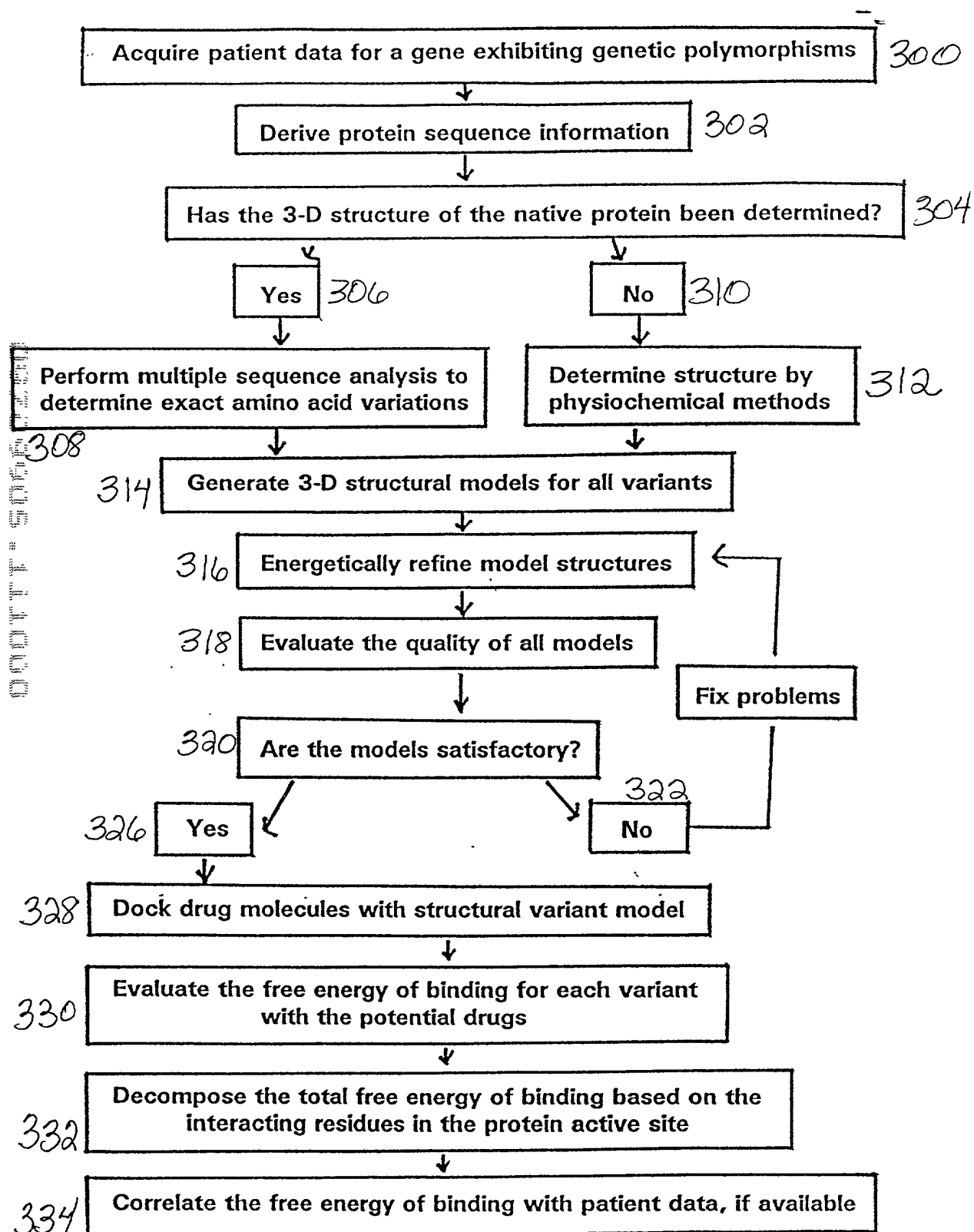
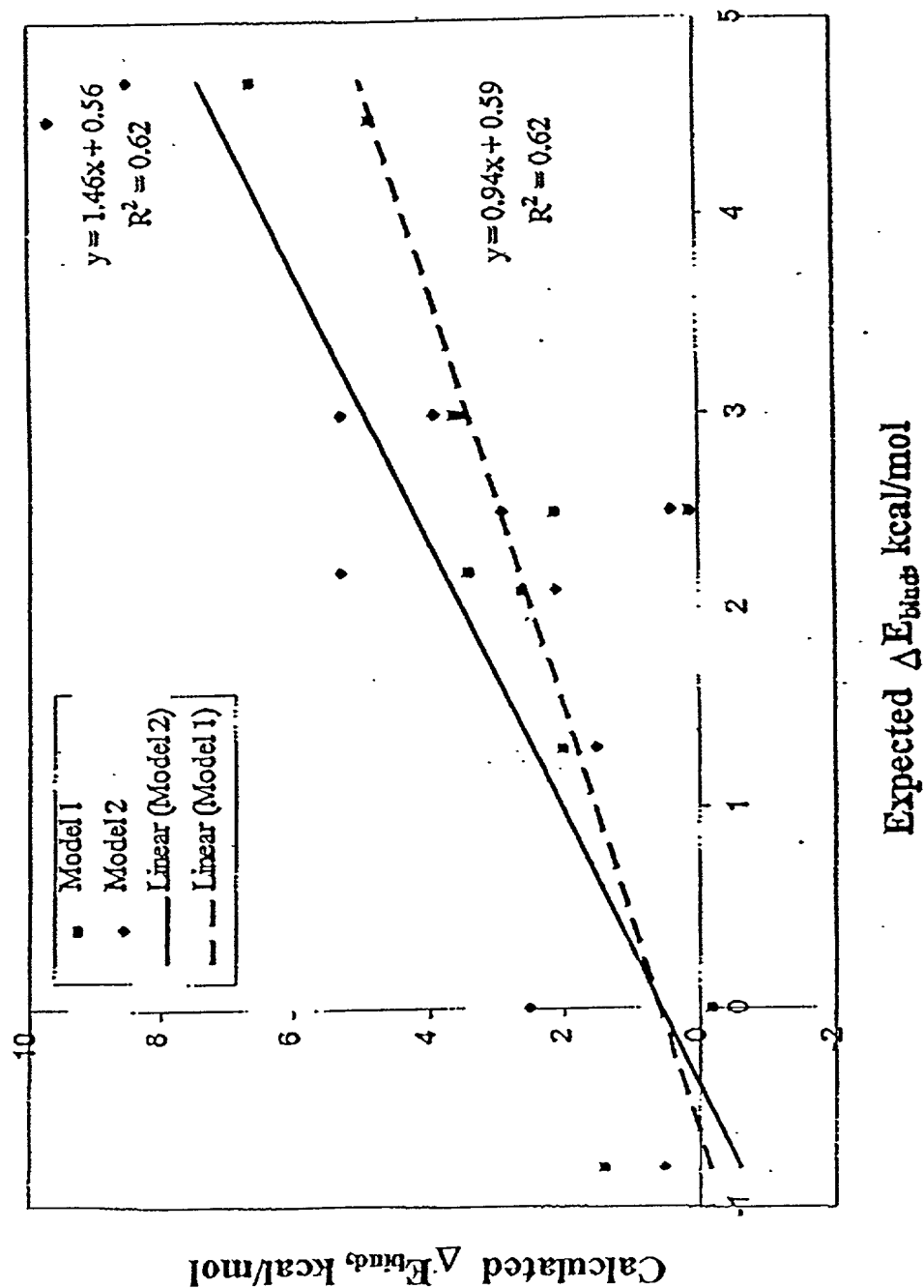


FIG. 3

Correlation between Experimental and Calculated Changes  
of Binding Energy upon Ligand Modifications in the Binding  
Site of NS3



# Comparison of Calculated versus Experimental Binding Free Energy Changes

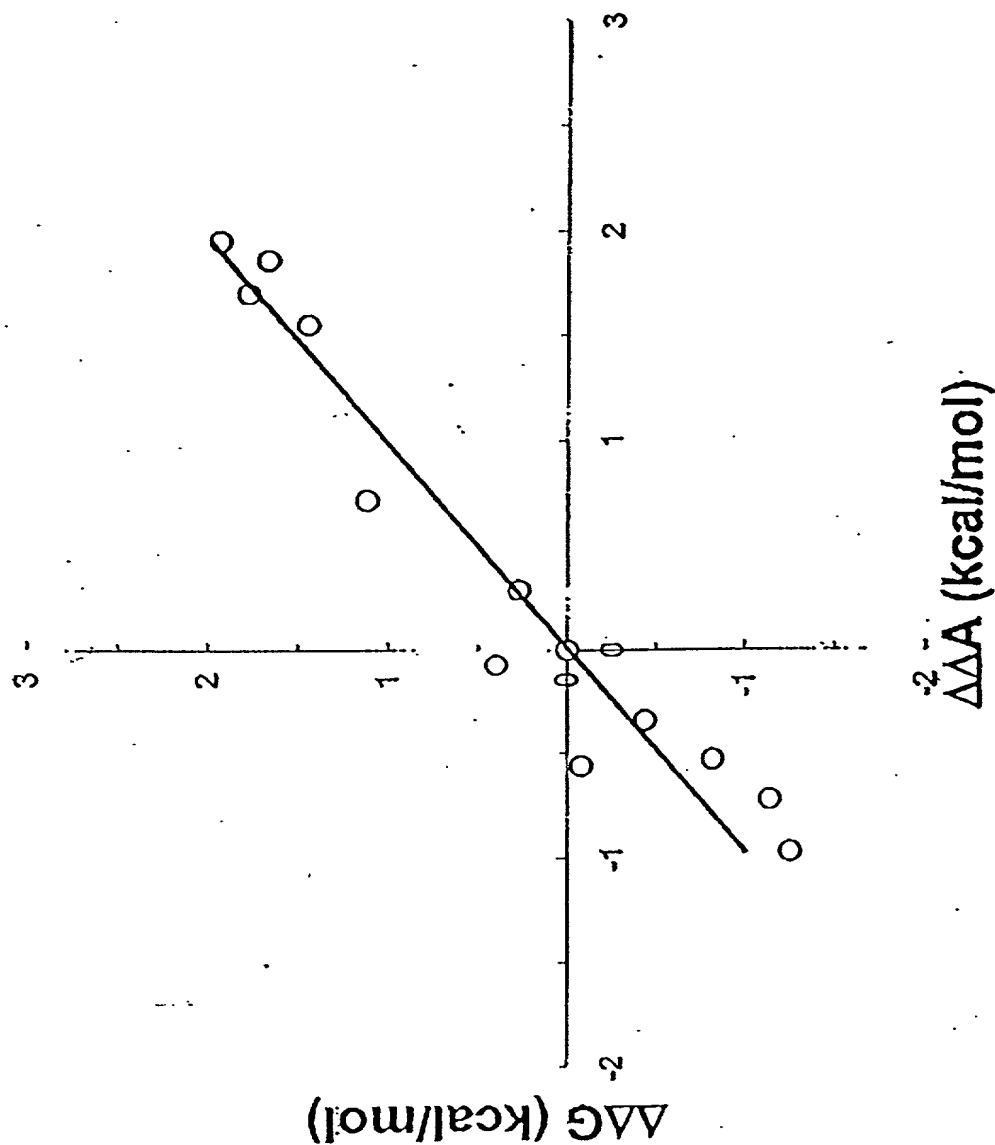
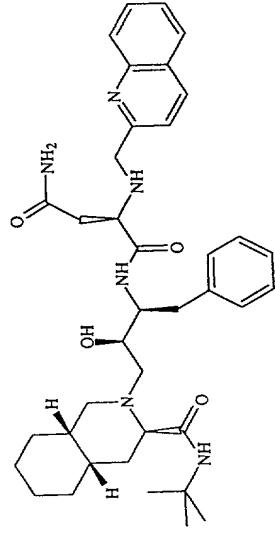
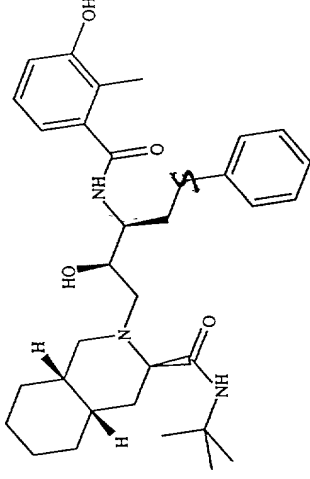


FIG. 5

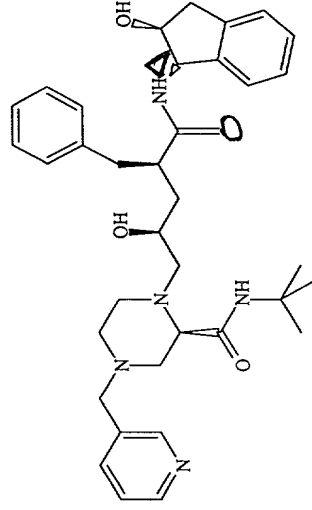
# HIV Protease Inhibitors Approved by FDA



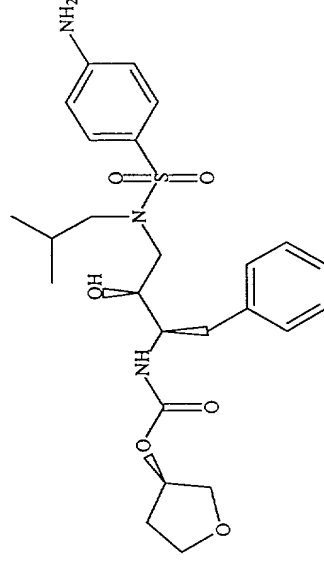
Saquinavir



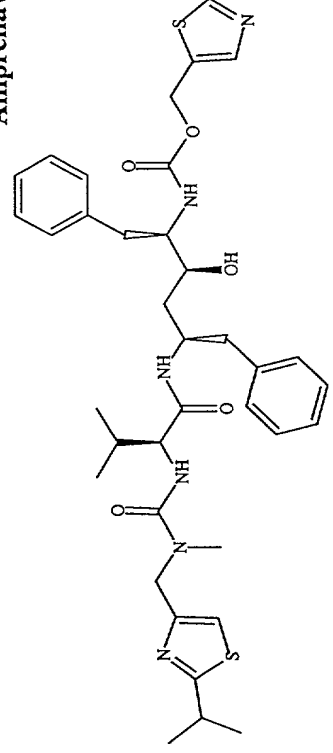
Nelfinavir



Indinavir

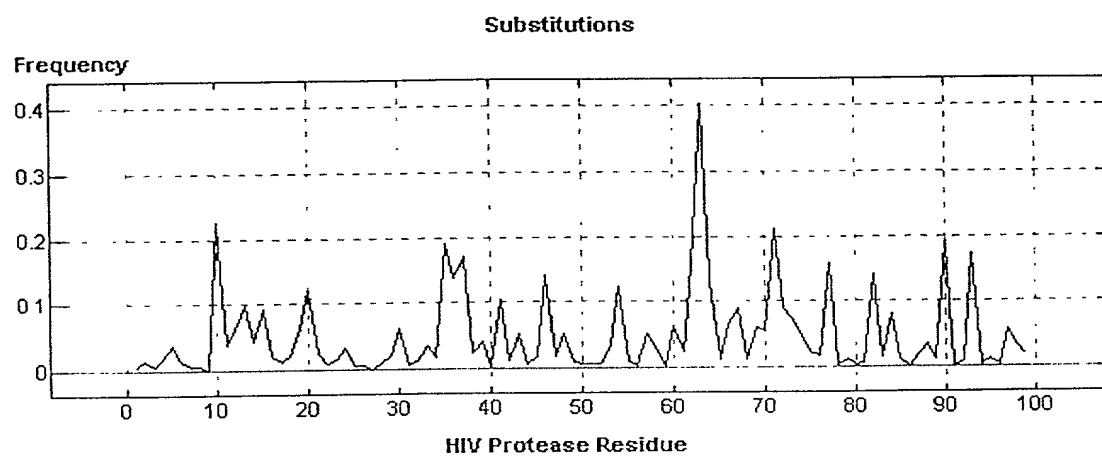


Amprenavir



Ritonavir

FIGURE 7















# Relationships

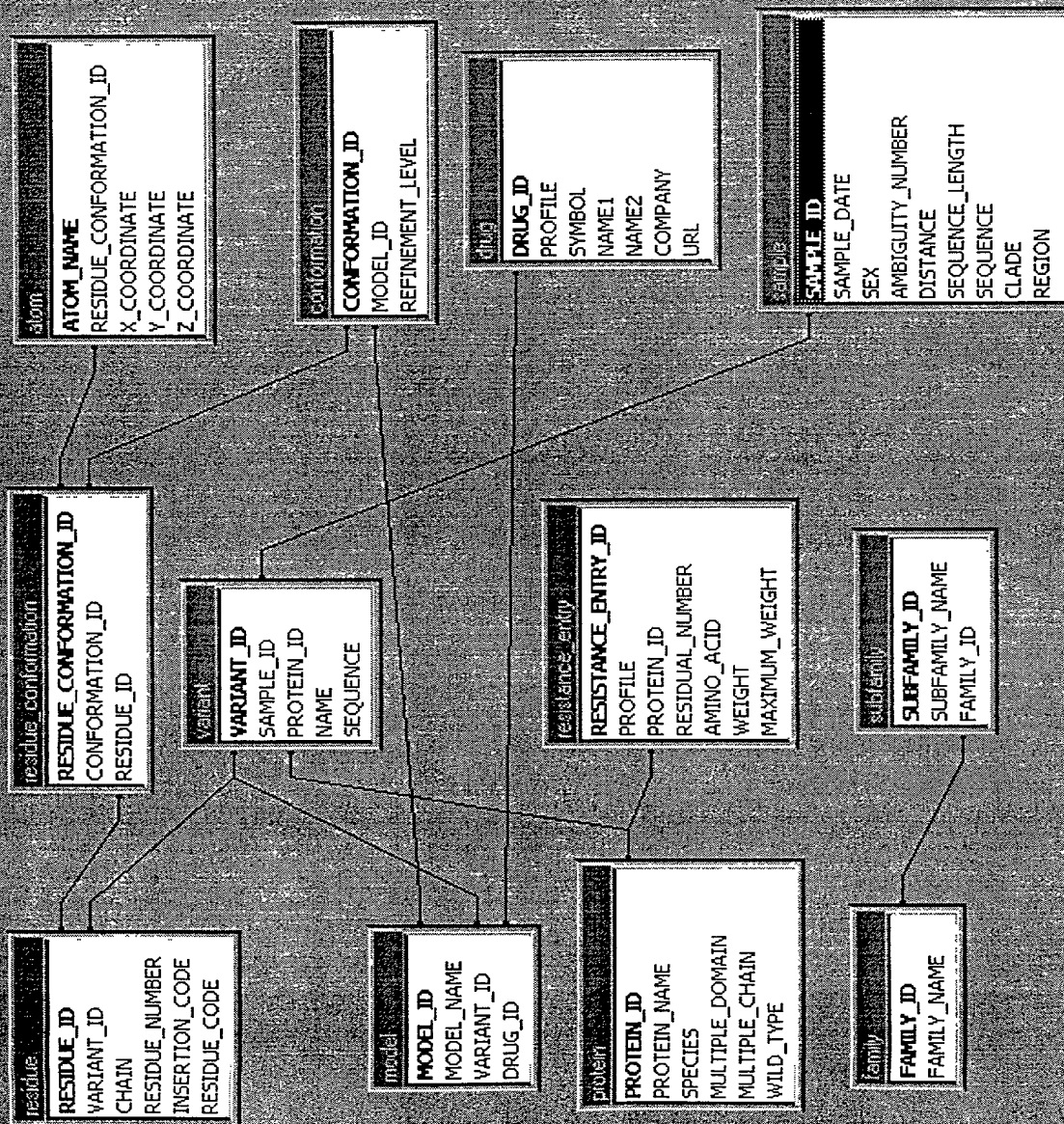


Figure 11A

ATOM	1	N	PRO	A	1	-3.433	7.956	34.152
ATOM	2	CA	PRO	A	1	-2.653	6.918	34.784
ATOM	3	C	PRO	A	1	-1.242	7.005	34.259
ATOM	4	O	PRO	A	1	-0.950	7.638	33.216
ATOM	5	CB	PRO	A	1	-3.281	5.601	34.262
ATOM	6	CG	PRO	A	1	-4.191	5.995	33.118
ATOM	7	CD	PRO	A	1	-4.547	7.461	33.339
ATOM	8	1H	PRO	A	1	-2.845	8.493	33.547
ATOM	9	2H	PRO	A	1	-3.824	8.552	34.853
ATOM	10	N	GLN	A	2	-0.259	6.464	35.001
ATOM	11	H	GLN	A	2	-0.475	6.057	35.889
ATOM	12	CA	GLN	A	2	1.115	6.443	34.568
ATOM	13	C	GLN	A	2	1.452	4.993	34.301
ATOM	14	O	GLN	A	2	1.379	4.106	35.173
ATOM	15	CB	GLN	A	2	2.070	6.966	35.653
ATOM	16	CG	GLN	A	2	3.549	6.859	35.240
ATOM	17	CD	GLN	A	2	4.490	7.744	36.054
ATOM	18	OE1	GLN	A	2	4.771	8.888	35.719
ATOM	19	NE2	GLN	A	2	4.980	7.190	37.144
ATOM	20	1HE2	GLN	A	2	5.605	7.702	37.734
ATOM	21	2HE2	GLN	A	2	4.731	6.253	37.390
ATOM	22	N	ILE	A	3	1.784	4.644	33.037
ATOM	23	H	ILE	A	3	1.876	5.351	32.336
ATOM	24	CA	ILE	A	3	2.013	3.257	32.665
ATOM	25	C	ILE	A	3	3.505	3.028	32.473
ATOM	26	O	ILE	A	3	4.242	3.777	31.787
ATOM	27	CB	ILE	A	3	1.226	2.944	31.370
ATOM	28	CG1	ILE	A	3	-0.274	3.239	31.603
ATOM	29	CG2	ILE	A	3	1.427	1.480	30.901
ATOM	30	CD1	ILE	A	3	-1.089	3.219	30.322
ATOM	31	N	THR	A	4	4.071	2.032	33.177
ATOM	32	H	THR	A	4	3.525	1.525	33.844
ATOM	33	CA	THR	A	4	5.451	1.661	33.007
ATOM	34	C	THR	A	4	5.515	0.637	31.901
ATOM	35	O	THR	A	4	4.490	0.143	31.397
ATOM	36	CB	THR	A	4	6.051	1.125	34.324
ATOM	37	OG1	THR	A	4	5.224	0.069	34.791
ATOM	38	HG1	THR	A	4	5.589	-0.299	35.646
ATOM	39	CG2	THR	A	4	6.085	2.212	35.431
ATOM	40	N	LEU	A	5	6.677	0.281	31.405
ATOM	41	H	LEU	A	5	7.518	0.530	31.885
ATOM	42	CA	LEU	A	5	6.754	-0.464	30.177
ATOM	43	C	LEU	A	5	7.432	-1.813	30.356
ATOM	44	O	LEU	A	5	7.940	-2.464	29.426
ATOM	45	CB	LEU	A	5	7.459	0.394	29.128
ATOM	46	CG	LEU	A	5	6.668	1.671	28.775
ATOM	47	CD1	LEU	A	5	7.493	2.649	27.939
ATOM	48	CD2	LEU	A	5	5.345	1.307	28.099
ATOM	49	N	TRP	A	6	7.420	-2.351	31.594
ATOM	50	H	TRP	A	6	7.030	-1.833	32.356
ATOM	51	CA	TRP	A	6	7.958	-3.669	31.865
ATOM	52	C	TRP	A	6	7.071	-4.697	31.204
ATOM	53	O	TRP	A	6	7.520	-5.798	30.828
ATOM	54	CB	TRP	A	6	8.099	-3.913	33.367
ATOM	55	CG	TRP	A	6	9.041	-2.974	34.070

Figure 11B

ATOM	56	CD1	TRP	A	6	8.745	-1.769	34.646
ATOM	57	CD2	TRP	A	6	10.449	-3.171	34.273
ATOM	58	NE1	TRP	A	6	9.875	-1.209	35.190
ATOM	59	HE1	TRP	A	6	9.930	-0.332	35.668
ATOM	60	CE2	TRP	A	6	10.932	-2.048	34.974
ATOM	61	CE3	TRP	A	6	11.334	-4.190	33.924
ATOM	62	CZ2	TRP	A	6	12.257	-1.917	35.333
ATOM	63	CZ3	TRP	A	6	12.650	-4.065	34.278
ATOM	64	CH2	TRP	A	6	13.106	-2.942	34.974
ATOM	65	N	GLN	A	7	5.773	-4.448	30.973
ATOM	66	H	GLN	A	7	5.354	-3.619	31.343
ATOM	67	CA	GLN	A	7	4.952	-5.339	30.205
ATOM	68	C	GLN	A	7	4.438	-4.569	29.033
ATOM	69	O	GLN	A	7	4.433	-3.321	29.000
ATOM	70	CB	GLN	A	7	3.712	-5.693	30.969
ATOM	71	CG	GLN	A	7	4.015	-6.467	32.210
ATOM	72	CD	GLN	A	7	2.734	-6.678	32.917
ATOM	73	OE1	GLN	A	7	2.053	-7.681	32.712
ATOM	74	NE2	GLN	A	7	2.356	-5.682	33.736
ATOM	75	1HE2	GLN	A	7	1.501	-5.748	34.251
ATOM	76	2HE2	GLN	A	7	2.926	-4.867	33.837
ATOM	77	N	ARG	A	8	3.777	-5.239	28.078
ATOM	78	H	ARG	A	8	3.688	-6.233	28.142
ATOM	79	CA	ARG	A	8	3.183	-4.568	26.948
ATOM	80	C	ARG	A	8	2.117	-3.648	27.461
ATOM	81	O	ARG	A	8	1.333	-3.965	28.387
ATOM	82	CB	ARG	A	8	2.574	-5.555	25.975
ATOM	83	CG	ARG	A	8	3.532	-6.593	25.437
ATOM	84	CD	ARG	A	8	2.842	-7.610	24.579
ATOM	85	NE	ARG	A	8	3.787	-8.487	23.900
ATOM	86	HE	ARG	A	8	4.762	-8.279	23.982
ATOM	87	CZ	ARG	A	8	3.405	-9.541	23.185
ATOM	88	NH1	ARG	A	8	2.125	-9.871	23.052
ATOM	89	2HH1	ARG	A	8	1.418	-9.321	23.496
ATOM	90	1HH1	ARG	A	8	1.869	-10.670	22.508
ATOM	91	NH2	ARG	A	8	4.332	-10.286	22.589
ATOM	92	1HH2	ARG	A	8	4.062	-11.082	22.048
ATOM	93	2HH2	ARG	A	8	5.299	-10.050	22.682
ATOM	94	N	PRO	A	9	1.990	-2.428	26.938
ATOM	95	CA	PRO	A	9	1.001	-1.462	27.440
ATOM	96	C	PRO	A	9	-0.365	-1.697	26.821
ATOM	97	O	PRO	A	9	-0.918	-0.935	26.008
ATOM	98	CB	PRO	A	9	1.572	-0.112	27.041
ATOM	99	CG	PRO	A	9	2.553	-0.404	25.931
ATOM	100	CD	PRO	A	9	3.024	-1.820	26.084
ATOM	101	N	LEU	A	10	-1.028	-2.803	27.227
ATOM	102	H	LEU	A	10	-0.616	-3.404	27.912
ATOM	103	CA	LEU	A	10	-2.319	-3.143	26.698
ATOM	104	C	LEU	A	10	-3.390	-2.565	27.591
ATOM	105	O	LEU	A	10	-3.336	-2.632	28.831
ATOM	106	CB	LEU	A	10	-2.451	-4.651	26.709
ATOM	107	CG	LEU	A	10	-1.483	-5.316	25.756
ATOM	108	CD1	LEU	A	10	-1.159	-6.740	26.212
ATOM	109	CD2	LEU	A	10	-2.083	-5.262	24.322
ATOM	110	N	VAL	A	11	-4.447	-1.952	27.033
ATOM	111	H	VAL	A	11	-4.507	-1.875	26.038

Query = 5954067

Figure 11c

ATOM	112	CA	VAL	A	11	-5.506	-1.398	27.835
ATOM	113	C	VAL	A	11	-6.827	-1.857	27.268
ATOM	114	O	VAL	A	11	-6.924	-2.490	26.198
ATOM	115	CB	VAL	A	11	-5.420	0.143	27.897
ATOM	116	CG1	VAL	A	11	-4.117	0.595	28.551
ATOM	117	CG2	VAL	A	11	-5.549	0.787	26.497
ATOM	118	N	THR	A	12	-7.954	-1.592	27.978
ATOM	119	H	THR	A	12	-7.884	-1.141	28.868
ATOM	120	CA	THR	A	12	-9.301	-1.942	27.496
ATOM	121	C	THR	A	12	-9.889	-0.726	26.795
ATOM	122	O	THR	A	12	-9.856	0.436	27.247
ATOM	123	CB	THR	A	12	-10.225	-2.385	28.659
ATOM	124	OG1	THR	A	12	-9.596	-3.458	29.338
ATOM	125	HG1	THR	A	12	-10.170	-3.766	30.096
ATOM	126	CG2	THR	A	12	-11.579	-2.895	28.156
ATOM	127	N	ILE	A	13	-10.449	-0.932	25.594
ATOM	128	H	ILE	A	13	-10.409	-1.841	25.178
ATOM	129	CA	ILE	A	13	-11.112	0.133	24.882
ATOM	130	C	ILE	A	13	-12.553	-0.292	24.693
ATOM	131	O	ILE	A	13	-12.935	-1.469	24.821
ATOM	132	CB	ILE	A	13	-10.432	0.364	23.511
ATOM	133	CG1	ILE	A	13	-10.466	-0.896	22.628
ATOM	134	CG2	ILE	A	13	-8.986	0.806	23.747
ATOM	135	CD1	ILE	A	13	-9.755	-0.745	21.294
ATOM	136	N	LYS	A	14	-13.470	0.658	24.438
ATOM	137	H	LYS	A	14	-13.209	1.622	24.481
ATOM	138	CA	LYS	A	14	-14.838	0.330	24.100
ATOM	139	C	LYS	A	14	-15.088	0.877	22.719
ATOM	140	O	LYS	A	14	-14.859	2.059	22.375
ATOM	141	CB	LYS	A	14	-15.855	0.916	25.099
ATOM	142	CG	LYS	A	14	-17.325	0.518	24.864
ATOM	143	CD	LYS	A	14	-18.078	0.146	26.166
ATOM	144	CE	LYS	A	14	-18.826	1.342	26.810
ATOM	145	NZ	LYS	A	14	-19.316	0.929	28.173
ATOM	146	1HZ	LYS	A	14	-19.801	1.693	28.599
ATOM	147	3HZ	LYS	A	14	-18.536	0.670	28.743
ATOM	148	2HZ	LYS	A	14	-19.936	0.150	28.082
ATOM	149	N	ILE	A	15	-15.535	0.005	21.798
ATOM	150	H	ILE	A	15	-15.806	-0.916	22.078
ATOM	151	CA	ILE	A	15	-15.642	0.347	20.400
ATOM	152	C	ILE	A	15	-16.894	-0.328	19.887
ATOM	153	O	ILE	A	15	-17.115	-1.542	20.041
ATOM	154	CB	ILE	A	15	-14.382	-0.132	19.639
ATOM	155	CG1	ILE	A	15	-14.478	0.148	18.125
ATOM	156	CG2	ILE	A	15	-14.082	-1.623	19.880
ATOM	157	CD1	ILE	A	15	-14.237	1.603	17.796
ATOM	158	N	GLY	A	16	-17.843	0.435	19.308
ATOM	159	H	GLY	A	16	-17.720	1.426	19.260
ATOM	160	CA	GLY	A	16	-19.053	-0.143	18.745
ATOM	161	C	GLY	A	16	-19.897	-0.817	19.789
ATOM	162	O	GLY	A	16	-20.774	-1.668	19.516
ATOM	163	N	GLY	A	17	-19.712	-0.493	21.088
ATOM	164	H	GLY	A	17	-19.038	0.204	21.334
ATOM	165	CA	GLY	A	17	-20.464	-1.126	22.160
ATOM	166	C	GLY	A	17	-19.718	-2.335	22.653
ATOM	167	O	GLY	A	17	-20.147	-3.098	23.540

Figure 11D

ATOM	168	N	GLN	A	18	-18.507	-2.591	22.121
ATOM	169	H	GLN	A	18	-18.059	-1.900	21.554
ATOM	170	CA	GLN	A	18	-17.806	-3.830	22.326
ATOM	171	C	GLN	A	18	-16.552	-3.549	23.123
ATOM	172	O	GLN	A	18	-15.887	-2.508	22.945
ATOM	173	CB	GLN	A	18	-17.393	-4.294	20.928
ATOM	174	CG	GLN	A	18	-16.911	-5.734	20.788
ATOM	175	CD	GLN	A	18	-18.018	-6.728	20.613
ATOM	176	OE1	GLN	A	18	-19.131	-6.574	21.152
ATOM	177	NE2	GLN	A	18	-17.722	-7.773	19.857
ATOM	178	1HE2	GLN	A	18	-18.404	-8.484	19.689
ATOM	179	2HE2	GLN	A	18	-16.814	-7.860	19.448
ATOM	180	N	LEU	A	19	-16.133	-4.397	24.087
ATOM	181	H	LEU	A	19	-16.682	-5.202	24.312
ATOM	182	CA	LEU	A	19	-14.909	-4.178	24.808
ATOM	183	C	LEU	A	19	-13.799	-4.912	24.090
ATOM	184	O	LEU	A	19	-13.989	-6.018	23.558
ATOM	185	CB	LEU	A	19	-14.982	-4.714	26.254
ATOM	186	CG	LEU	A	19	-15.490	-3.778	27.374
ATOM	187	CD1	LEU	A	19	-16.392	-2.639	26.856
ATOM	188	CD2	LEU	A	19	-16.208	-4.516	28.465
ATOM	189	N	LYS	A	20	-12.603	-4.372	23.978
ATOM	190	H	LYS	A	20	-12.442	-3.448	24.324
ATOM	191	CA	LYS	A	20	-11.507	-5.082	23.365
ATOM	192	C	LYS	A	20	-10.266	-4.618	24.062
ATOM	193	O	LYS	A	20	-10.228	-3.611	24.816
ATOM	194	CB	LYS	A	20	-11.397	-4.798	21.875
ATOM	195	CG	LYS	A	20	-12.558	-5.356	21.100
ATOM	196	CD	LYS	A	20	-12.537	-4.988	19.615
ATOM	197	CE	LYS	A	20	-13.414	-5.958	18.827
ATOM	198	NZ	LYS	A	20	-12.681	-7.208	18.639
ATOM	199	1HZ	LYS	A	20	-13.247	-7.852	18.123
ATOM	200	3HZ	LYS	A	20	-12.458	-7.601	19.531
ATOM	201	2HZ	LYS	A	20	-11.837	-7.027	18.134
ATOM	202	N	GLU	A	21	-9.150	-5.357	23.893
ATOM	203	H	GLU	A	21	-9.185	-6.188	23.338
ATOM	204	CA	GLU	A	21	-7.890	-4.997	24.486
ATOM	205	C	GLU	A	21	-7.001	-4.462	23.390
ATOM	206	O	GLU	A	21	-6.970	-4.992	22.258
ATOM	207	CB	GLU	A	21	-7.268	-6.260	25.051
ATOM	208	CG	GLU	A	21	-5.835	-6.140	25.480
ATOM	209	CD	GLU	A	21	-5.405	-7.352	26.275
ATOM	210	OE1	GLU	A	21	-5.624	-7.343	27.508
ATOM	211	OE2	GLU	A	21	-4.852	-8.309	25.684
ATOM	212	N	ALA	A	22	-6.239	-3.369	23.595
ATOM	213	H	ALA	A	22	-6.223	-2.938	24.497
ATOM	214	CA	ALA	A	22	-5.419	-2.781	22.520
ATOM	215	C	ALA	A	22	-4.138	-2.255	23.114
ATOM	216	O	ALA	A	22	-3.985	-1.914	24.314
ATOM	217	CB	ALA	A	22	-6.134	-1.657	21.821
ATOM	218	N	LEU	A	23	-3.121	-2.091	22.240
ATOM	219	H	LEU	A	23	-3.279	-2.236	21.263
ATOM	220	CA	LEU	A	23	-1.797	-1.712	22.640
ATOM	221	C	LEU	A	23	-1.660	-0.230	22.443
ATOM	222	O	LEU	A	23	-2.020	0.349	21.402
ATOM	223	CB	LEU	A	23	-0.814	-2.486	21.732





ATOM	224	CG	LEU	A	23	0.705	-2.448	21.991
ATOM	225	CD1	LEU	A	23	1.088	-3.400	23.124
ATOM	226	CD2	LEU	A	23	1.462	-2.878	20.708
ATOM	227	N	LEU	A	24	-1.192	0.530	23.463
ATOM	228	H	LEU	A	24	-1.015	0.110	24.353
ATOM	229	CA	LEU	A	24	-0.935	1.952	23.305
ATOM	230	C	LEU	A	24	0.403	2.089	22.609
ATOM	231	O	LEU	A	24	1.471	1.717	23.130
ATOM	232	CB	LEU	A	24	-0.921	2.609	24.681
ATOM	233	CG	LEU	A	24	-2.220	2.492	25.477
ATOM	234	CD1	LEU	A	24	-2.063	3.291	26.772
ATOM	235	CD2	LEU	A	24	-3.419	3.000	24.691
ATOM	236	N	ASP	A	25	0.454	2.590	21.397
ATOM	237	H	ASP	A	25	-0.334	3.085	21.032
ATOM	238	CA	ASP	A	25	1.642	2.423	20.605
ATOM	239	C	ASP	A	25	2.130	3.750	20.059
ATOM	240	O	ASP	A	25	1.568	4.320	19.110
ATOM	241	CB	ASP	A	25	1.263	1.435	19.486
ATOM	242	CG	ASP	A	25	2.428	1.051	18.561
ATOM	243	OD1	ASP	A	25	3.546	1.540	18.729
ATOM	244	OD2	ASP	A	25	2.164	0.241	17.658
ATOM	245	N	THR	A	26	3.203	4.337	20.605
ATOM	246	H	THR	A	26	3.694	3.880	21.346
ATOM	247	CA	THR	A	26	3.691	5.652	20.144
ATOM	248	C	THR	A	26	4.397	5.583	18.778
ATOM	249	O	THR	A	26	4.642	6.587	18.079
ATOM	250	CB	THR	A	26	4.596	6.219	21.217
ATOM	251	OG1	THR	A	26	5.716	5.324	21.386
ATOM	252	HG1	THR	A	26	6.332	5.676	22.091
ATOM	253	CG2	THR	A	26	3.878	6.320	22.577
ATOM	254	N	GLY	A	27	4.757	4.377	18.298
ATOM	255	H	GLY	A	27	4.526	3.550	18.811
ATOM	256	CA	GLY	A	27	5.481	4.233	17.040
ATOM	257	C	GLY	A	27	4.520	4.190	15.886
ATOM	258	O	GLY	A	27	4.908	4.242	14.696
ATOM	259	N	ALA	A	28	3.197	4.084	16.117
ATOM	260	H	ALA	A	28	2.856	4.091	17.057
ATOM	261	CA	ALA	A	28	2.213	3.955	15.018
ATOM	262	C	ALA	A	28	1.598	5.299	14.750
ATOM	263	O	ALA	A	28	1.062	5.982	15.650
ATOM	264	CB	ALA	A	28	1.117	2.980	15.390
ATOM	265	N	ASP	A	29	1.503	5.744	13.490
ATOM	266	H	ASP	A	29	1.912	5.216	12.746
ATOM	267	CA	ASP	A	29	0.810	6.984	13.213
ATOM	268	C	ASP	A	29	-0.666	6.724	13.327
ATOM	269	O	ASP	A	29	-1.488	7.637	13.568
ATOM	270	CB	ASP	A	29	1.009	7.433	11.775
ATOM	271	CG	ASP	A	29	2.439	7.882	11.412
ATOM	272	OD1	ASP	A	29	3.360	7.856	12.269
ATOM	273	OD2	ASP	A	29	2.606	8.253	10.252
ATOM	274	N	ASP	A	30	-1.143	5.517	12.990
ATOM	275	H	ASP	A	30	-0.508	4.769	12.800
ATOM	276	CA	ASP	A	30	-2.579	5.245	12.887
ATOM	277	C	ASP	A	30	-3.057	4.208	13.867
ATOM	278	O	ASP	A	30	-2.284	3.483	14.546
ATOM	279	CB	ASP	A	30	-2.896	4.758	11.456

Figure 11F

ORTEP displacement ellipsoids

ATOM	280	CG	ASP	A	30	-2.495	5.768	10.425
ATOM	281	OD1	ASP	A	30	-3.067	6.871	10.423
ATOM	282	OD2	ASP	A	30	-1.596	5.494	9.618
ATOM	283	N	THR	A	31	-4.393	4.076	14.002
ATOM	284	H	THR	A	31	-5.004	4.700	13.515
ATOM	285	CA	THR	A	31	-5.059	3.062	14.829
ATOM	286	C	THR	A	31	-5.565	1.967	13.913
ATOM	287	O	THR	A	31	-6.223	2.169	12.870
ATOM	288	CB	THR	A	31	-6.212	3.725	15.566
ATOM	289	OG1	THR	A	31	-5.668	4.667	16.474
ATOM	290	HG1	THR	A	31	-6.403	5.122	16.976
ATOM	291	CG2	THR	A	31	-7.044	2.702	16.389
ATOM	292	N	VAL	A	32	-5.187	0.713	14.235
ATOM	293	H	VAL	A	32	-4.649	0.555	15.063
ATOM	294	CA	VAL	A	32	-5.517	-0.462	13.437
ATOM	295	C	VAL	A	32	-6.092	-1.506	14.365
ATOM	296	O	VAL	A	32	-5.502	-1.957	15.365
ATOM	297	CB	VAL	A	32	-4.260	-1.064	12.757
ATOM	298	CG1	VAL	A	32	-4.667	-2.136	11.735
ATOM	299	CG2	VAL	A	32	-3.422	0.017	12.032
ATOM	300	N	LEU	A	33	-7.352	-1.923	14.119
ATOM	301	H	LEU	A	33	-7.867	-1.523	13.361
ATOM	302	CA	LEU	A	33	-7.982	-2.940	14.929
ATOM	303	C	LEU	A	33	-8.174	-4.203	14.107
ATOM	304	O	LEU	A	33	-8.268	-4.247	12.853
ATOM	305	CB	LEU	A	33	-9.336	-2.477	15.408
ATOM	306	CG	LEU	A	33	-9.292	-1.149	16.127
ATOM	307	CD1	LEU	A	33	-10.710	-0.747	16.485
ATOM	308	CD2	LEU	A	33	-8.348	-1.139	17.347
ATOM	309	N	GLU	A	34	-8.296	-5.319	14.782
ATOM	310	H	GLU	A	34	-8.244	-5.302	15.780
ATOM	311	CA	GLU	A	34	-8.503	-6.551	14.086
ATOM	312	C	GLU	A	34	-9.909	-6.549	13.510
ATOM	313	O	GLU	A	34	-10.808	-5.717	13.795
ATOM	314	CB	GLU	A	34	-8.265	-7.750	15.010
ATOM	315	CG	GLU	A	34	-9.259	-7.791	16.165
ATOM	316	CD	GLU	A	34	-8.763	-8.552	17.404
ATOM	317	OE1	GLU	A	34	-7.670	-9.193	17.368
ATOM	318	OE2	GLU	A	34	-9.482	-8.497	18.407
ATOM	319	N	GLU	A	35	-10.152	-7.480	12.568
ATOM	320	H	GLU	A	35	-9.485	-8.208	12.407
ATOM	321	CA	GLU	A	35	-11.352	-7.466	11.773
ATOM	322	C	GLU	A	35	-12.631	-7.520	12.571
ATOM	323	O	GLU	A	35	-12.814	-8.294	13.528
ATOM	324	CB	GLU	A	35	-11.237	-8.536	10.707
ATOM	325	CG	GLU	A	35	-9.945	-8.280	9.907
ATOM	326	CD	GLU	A	35	-9.872	-8.872	8.486
ATOM	327	OE1	GLU	A	35	-10.612	-8.401	7.603
ATOM	328	OE2	GLU	A	35	-9.024	-9.776	8.261
ATOM	329	N	MET	A	36	-13.580	-6.598	12.278
ATOM	330	H	MET	A	36	-13.439	-5.967	11.515
ATOM	331	CA	MET	A	36	-14.819	-6.495	13.052
ATOM	332	C	MET	A	36	-15.826	-5.635	12.271
ATOM	333	O	MET	A	36	-15.514	-4.828	11.371
ATOM	334	CB	MET	A	36	-14.593	-5.845	14.428
ATOM	335	CG	MET	A	36	-14.279	-4.353	14.417

Figure 11G

ATOM	336	SD	MET	A	36	-14.251	-3.718	16.099
ATOM	337	CE	MET	A	36	-12.487	-3.846	16.409
ATOM	338	N	SER	A	37	-17.130	-5.776	12.590
ATOM	339	H	SER	A	37	-17.399	-6.431	13.296
ATOM	340	CA	SER	A	37	-18.155	-5.005	11.940
ATOM	341	C	SER	A	37	-18.286	-3.693	12.657
ATOM	342	O	SER	A	37	-18.593	-3.624	13.865
ATOM	343	CB	SER	A	37	-19.506	-5.688	12.032
ATOM	344	OG	SER	A	37	-19.455	-7.054	11.716
ATOM	345	HG	SER	A	37	-20.367	-7.457	11.791
ATOM	346	N	LEU	A	38	-18.185	-2.569	11.933
ATOM	347	H	LEU	A	38	-17.956	-2.625	10.952
ATOM	348	CA	LEU	A	38	-18.557	-1.247	12.465
ATOM	349	C	LEU	A	38	-19.630	-0.605	11.572
ATOM	350	O	LEU	A	38	-19.706	-0.939	10.391
ATOM	351	CB	LEU	A	38	-17.315	-0.346	12.588
ATOM	352	CG	LEU	A	38	-16.246	-0.818	13.596
ATOM	353	CD1	LEU	A	38	-14.998	0.073	13.489
ATOM	354	CD2	LEU	A	38	-16.756	-0.787	15.046
ATOM	355	N	PRO	A	39	-20.455	0.321	12.108
ATOM	356	CA	PRO	A	39	-21.460	1.053	11.339
ATOM	357	C	PRO	A	39	-20.824	2.176	10.502
ATOM	358	O	PRO	A	39	-19.654	2.519	10.685
ATOM	359	CB	PRO	A	39	-22.430	1.607	12.389
ATOM	360	CG	PRO	A	39	-21.531	1.845	13.600
ATOM	361	CD	PRO	A	39	-20.539	0.686	13.517
ATOM	362	N	GLY	A	40	-21.620	2.749	9.586
ATOM	363	H	GLY	A	40	-22.569	2.417	9.493
ATOM	364	CA	GLY	A	40	-21.203	3.811	8.678
ATOM	365	C	GLY	A	40	-20.836	3.262	7.298
ATOM	366	O	GLY	A	40	-21.405	2.268	6.845
ATOM	367	N	LYS	A	41	-19.895	3.945	6.631
ATOM	368	H	LYS	A	41	-19.496	4.761	7.071
ATOM	369	CA	LYS	A	41	-19.323	3.558	5.343
ATOM	370	C	LYS	A	41	-17.798	3.757	5.371
ATOM	371	O	LYS	A	41	-17.263	4.462	6.229
ATOM	372	CB	LYS	A	41	-20.025	4.352	4.224
ATOM	373	CG	LYS	A	41	-19.703	3.839	2.810
ATOM	374	CD	LYS	A	41	-20.610	4.486	1.757
ATOM	375	CE	LYS	A	41	-20.240	3.964	0.366
ATOM	376	NZ	LYS	A	41	-21.097	4.552	-0.678
ATOM	377	1HZ	LYS	A	41	-20.824	4.189	-1.580
ATOM	378	3HZ	LYS	A	41	-20.993	5.556	-0.673
ATOM	379	2HZ	LYS	A	41	-22.061	4.311	-0.498
ATOM	380	N	TRP	A	42	-17.104	3.091	4.439
ATOM	381	H	TRP	A	42	-17.620	2.548	3.762
ATOM	382	CA	TRP	A	42	-15.654	2.932	4.423
ATOM	383	C	TRP	A	42	-15.105	2.852	2.994
ATOM	384	O	TRP	A	42	-15.845	2.702	2.021
ATOM	385	CB	TRP	A	42	-15.279	1.675	5.236
ATOM	386	CG	TRP	A	42	-16.214	0.514	5.094
ATOM	387	CD1	TRP	A	42	-16.230	-0.402	4.101
ATOM	388	CD2	TRP	A	42	-17.355	0.203	5.942
ATOM	389	NE1	TRP	A	42	-17.297	-1.260	4.281
ATOM	390	HE1	TRP	A	42	-17.504	-2.015	3.644
ATOM	391	CE2	TRP	A	42	-18.045	-0.914	5.389

Figure 11H

ATOM	392	CE3	TRP	A	42	-17.896	0.792	7.103
ATOM	393	CZ2	TRP	A	42	-19.224	-1.421	5.959
ATOM	394	CZ3	TRP	A	42	-19.077	0.298	7.675
ATOM	395	CH2	TRP	A	42	-19.741	-0.806	7.112
ATOM	396	N	LYS	A	43	-13.771	2.932	2.911
ATOM	397	H	LYS	A	43	-13.260	3.058	3.773
ATOM	398	CA	LYS	A	43	-12.951	2.802	1.713
ATOM	399	C	LYS	A	43	-11.773	1.859	2.012
ATOM	400	O	LYS	A	43	-11.359	1.760	3.166
ATOM	401	CB	LYS	A	43	-12.451	4.193	1.270
ATOM	402	CG	LYS	A	43	-11.724	4.979	2.383
ATOM	403	CD	LYS	A	43	-11.060	6.267	1.873
ATOM	404	CE	LYS	A	43	-9.784	6.001	1.065
ATOM	405	NZ	LYS	A	43	-8.700	5.458	1.903
ATOM	406	1HZ	LYS	A	43	-7.876	5.315	1.338
ATOM	407	3HZ	LYS	A	43	-8.993	4.576	2.300
ATOM	408	2HZ	LYS	A	43	-8.493	6.108	2.647
ATOM	409	N	PRO	A	44	-11.177	1.197	1.004
ATOM	410	CA	PRO	A	44	-9.947	0.435	1.187
ATOM	411	C	PRO	A	44	-8.760	1.392	1.379
ATOM	412	O	PRO	A	44	-8.711	2.434	0.720
ATOM	413	CB	PRO	A	44	-9.808	-0.393	-0.095
ATOM	414	CG	PRO	A	44	-10.501	0.458	-1.159
ATOM	415	CD	PRO	A	44	-11.630	1.132	-0.380
ATOM	416	N	LYS	A	45	-7.790	1.030	2.240
ATOM	417	H	LYS	A	45	-7.912	0.227	2.824
ATOM	418	CA	LYS	A	45	-6.547	1.747	2.314
ATOM	419	C	LYS	A	45	-5.493	0.683	2.507
ATOM	420	O	LYS	A	45	-5.780	-0.470	2.869
ATOM	421	CB	LYS	A	45	-6.594	2.699	3.524
ATOM	422	CG	LYS	A	45	-5.463	3.744	3.609
ATOM	423	CD	LYS	A	45	-5.340	4.289	5.052
ATOM	424	CE	LYS	A	45	-4.262	5.383	5.204
ATOM	425	NZ	LYS	A	45	-2.907	4.911	4.916
ATOM	426	1HZ	LYS	A	45	-2.260	5.664	5.032
ATOM	427	3HZ	LYS	A	45	-2.864	4.577	3.975
ATOM	428	2HZ	LYS	A	45	-2.672	4.169	5.544
ATOM	429	N	MET	A	46	-4.224	0.949	2.193
ATOM	430	H	MET	A	46	-3.998	1.805	1.728
ATOM	431	CA	MET	A	46	-3.157	0.027	2.509
ATOM	432	C	MET	A	46	-2.417	0.701	3.627
ATOM	433	O	MET	A	46	-2.259	1.937	3.634
ATOM	434	CB	MET	A	46	-2.166	-0.088	1.379
ATOM	435	CG	MET	A	46	-2.782	-0.366	0.053
ATOM	436	SD	MET	A	46	-3.076	-2.108	-0.118
ATOM	437	CE	MET	A	46	-1.417	-2.652	-0.186
ATOM	438	N	ILE	A	47	-1.827	-0.016	4.586
ATOM	439	H	ILE	A	47	-2.010	-0.997	4.655
ATOM	440	CA	ILE	A	47	-0.922	0.586	5.539
ATOM	441	C	ILE	A	47	0.233	-0.372	5.654
ATOM	442	O	ILE	A	47	0.135	-1.584	5.356
ATOM	443	CB	ILE	A	47	-1.550	0.836	6.923
ATOM	444	CG1	ILE	A	47	-2.459	-0.301	7.354
ATOM	445	CG2	ILE	A	47	-2.248	2.164	6.995
ATOM	446	CD1	ILE	A	47	-1.724	-1.336	8.111
ATOM	447	N	GLY	A	48	1.420	0.089	6.043

Figure 11

PDB ID: 4D6E

ATOM	448	H	GLY	A	48	1.509	1.040	6.339
ATOM	449	CA	GLY	A	48	2.584	-0.753	6.048
ATOM	450	C	GLY	A	48	3.280	-0.657	7.376
ATOM	451	O	GLY	A	48	3.050	0.190	8.265
ATOM	452	N	GLY	A	49	4.197	-1.617	7.603
ATOM	453	H	GLY	A	49	4.375	-2.308	6.902
ATOM	454	CA	GLY	A	49	4.936	-1.684	8.828
ATOM	455	C	GLY	A	49	6.105	-2.589	8.533
ATOM	456	O	GLY	A	49	6.482	-2.807	7.370
ATOM	457	N	ILE	A	50	6.761	-3.173	9.552
ATOM	458	H	ILE	A	50	6.552	-2.908	10.493
ATOM	459	CA	ILE	A	50	7.772	-4.184	9.344
ATOM	460	C	ILE	A	50	7.148	-5.317	8.566
ATOM	461	O	ILE	A	50	5.981	-5.734	8.772
ATOM	462	CB	ILE	A	50	8.258	-4.686	10.722
ATOM	463	CG1	ILE	A	50	9.257	-3.714	11.382
ATOM	464	CG2	ILE	A	50	8.813	-6.134	10.693
ATOM	465	CD1	ILE	A	50	10.580	-3.498	10.628
ATOM	466	N	GLY	A	51	7.847	-5.891	7.596
ATOM	467	H	GLY	A	51	8.772	-5.569	7.395
ATOM	468	CA	GLY	A	51	7.265	-6.966	6.850
ATOM	469	C	GLY	A	51	6.519	-6.559	5.591
ATOM	470	O	GLY	A	51	6.430	-7.318	4.634
ATOM	471	N	GLY	A	52	5.886	-5.375	5.517
ATOM	472	H	GLY	A	52	5.990	-4.710	6.257
ATOM	473	CA	GLY	A	52	5.108	-5.227	4.320
ATOM	474	C	GLY	A	52	3.832	-4.415	4.516
ATOM	475	O	GLY	A	52	3.654	-3.624	5.467
ATOM	476	N	PHE	A	53	2.886	-4.518	3.559
ATOM	477	H	PHE	A	53	3.013	-5.161	2.804
ATOM	478	CA	PHE	A	53	1.653	-3.720	3.566
ATOM	479	C	PHE	A	53	0.494	-4.651	3.783
ATOM	480	O	PHE	A	53	0.448	-5.816	3.336
ATOM	481	CB	PHE	A	53	1.424	-3.022	2.221
ATOM	482	CG	PHE	A	53	2.363	-1.896	2.008
ATOM	483	CD1	PHE	A	53	3.615	-2.135	1.447
ATOM	484	CD2	PHE	A	53	2.011	-0.608	2.414
ATOM	485	CE1	PHE	A	53	4.514	-1.087	1.275
ATOM	486	CE2	PHE	A	53	2.925	0.446	2.237
ATOM	487	CZ	PHE	A	53	4.172	0.202	1.668
ATOM	488	N	ILE	A	54	-0.554	-4.173	4.439
ATOM	489	H	ILE	A	54	-0.491	-3.285	4.895
ATOM	490	CA	ILE	A	54	-1.789	-4.911	4.509
ATOM	491	C	ILE	A	54	-2.903	-3.995	4.033
ATOM	492	O	ILE	A	54	-2.751	-2.770	3.855
ATOM	493	CB	ILE	A	54	-2.034	-5.535	5.904
ATOM	494	CG1	ILE	A	54	-2.343	-4.481	6.988
ATOM	495	CG2	ILE	A	54	-0.799	-6.318	6.314
ATOM	496	CD1	ILE	A	54	-3.010	-5.089	8.246
ATOM	497	N	LYS	A	55	-4.029	-4.577	3.560
ATOM	498	H	LYS	A	55	-4.084	-5.574	3.501
ATOM	499	CA	LYS	A	55	-5.177	-3.798	3.129
ATOM	500	C	LYS	A	55	-6.115	-3.726	4.300
ATOM	501	O	LYS	A	55	-6.422	-4.707	5.023
ATOM	502	CB	LYS	A	55	-5.928	-4.461	1.938
ATOM	503	CG	LYS	A	55	-6.853	-3.547	1.106

Figure 11<sub>J</sub>

ATOM	504	CD	LYS	A	55	-8.267	-3.332	1.714
ATOM	505	CE	LYS	A	55	-9.303	-4.392	1.301
ATOM	506	NZ	LYS	A	55	-10.521	-4.453	2.192
ATOM	507	1HZ	LYS	A	55	-11.142	-5.162	1.859
ATOM	508	3HZ	LYS	A	55	-10.987	-3.569	2.180
ATOM	509	2HZ	LYS	A	55	-10.240	-4.669	3.127
ATOM	510	N	VAL	A	56	-6.599	-2.509	4.619
ATOM	511	H	VAL	A	56	-6.337	-1.713	4.073
ATOM	512	CA	VAL	A	56	-7.494	-2.311	5.735
ATOM	513	C	VAL	A	56	-8.711	-1.584	5.236
ATOM	514	O	VAL	A	56	-8.767	-1.029	4.114
ATOM	515	CB	VAL	A	56	-6.759	-1.475	6.812
ATOM	516	CG1	VAL	A	56	-5.569	-2.209	7.385
ATOM	517	CG2	VAL	A	56	-6.287	-0.108	6.268
ATOM	518	N	ARG	A	57	-9.784	-1.539	6.005
ATOM	519	H	ARG	A	57	-9.835	-2.117	6.819
ATOM	520	CA	ARG	A	57	-10.855	-0.648	5.638
ATOM	521	C	ARG	A	57	-10.738	0.534	6.554
ATOM	522	O	ARG	A	57	-10.558	0.449	7.789
ATOM	523	CB	ARG	A	57	-12.219	-1.271	5.835
ATOM	524	CG	ARG	A	57	-12.480	-2.452	4.952
ATOM	525	CD	ARG	A	57	-13.834	-3.051	5.195
ATOM	526	NE	ARG	A	57	-14.122	-4.137	4.270
ATOM	527	HE	ARG	A	57	-13.442	-4.347	3.568
ATOM	528	CZ	ARG	A	57	-15.243	-4.851	4.324
ATOM	529	NH1	ARG	A	57	-16.175	-4.624	5.243
ATOM	530	2HH1	ARG	A	57	-16.044	-3.899	5.920
ATOM	531	1HH1	ARG	A	57	-17.008	-5.178	5.258
ATOM	532	NH2	ARG	A	57	-15.433	-5.822	3.434
ATOM	533	1HH2	ARG	A	57	-16.270	-6.368	3.461
ATOM	534	2HH2	ARG	A	57	-14.738	-6.006	2.738
ATOM	535	N	GLN	A	58	-10.881	1.741	6.036
ATOM	536	H	GLN	A	58	-11.030	1.844	5.053
ATOM	537	CA	GLN	A	58	-10.830	2.922	6.839
ATOM	538	C	GLN	A	58	-12.231	3.342	7.205
ATOM	539	O	GLN	A	58	-13.106	3.608	6.359
ATOM	540	CB	GLN	A	58	-10.208	4.038	6.030
ATOM	541	CG	GLN	A	58	-10.055	5.293	6.817
ATOM	542	CD	GLN	A	58	-9.632	6.411	5.927
ATOM	543	OE1	GLN	A	58	-10.379	7.334	5.662
ATOM	544	NE2	GLN	A	58	-8.412	6.303	5.437
ATOM	545	1HE2	GLN	A	58	-8.047	7.009	4.830
ATOM	546	2HE2	GLN	A	58	-7.843	5.514	5.668
ATOM	547	N	TYR	A	59	-12.527	3.516	8.509
ATOM	548	H	TYR	A	59	-11.877	3.219	9.209
ATOM	549	CA	TYR	A	59	-13.769	4.125	8.933
ATOM	550	C	TYR	A	59	-13.411	5.452	9.565
ATOM	551	O	TYR	A	59	-12.416	5.592	10.310
ATOM	552	CB	TYR	A	59	-14.517	3.252	9.957
ATOM	553	CG	TYR	A	59	-14.287	1.770	9.723
ATOM	554	CD1	TYR	A	59	-13.007	1.269	9.457
ATOM	555	CD2	TYR	A	59	-15.346	0.865	9.766
ATOM	556	CE1	TYR	A	59	-12.797	-0.092	9.240
ATOM	557	CE2	TYR	A	59	-15.148	-0.494	9.551
ATOM	558	CZ	TYR	A	59	-13.873	-0.972	9.287
ATOM	559	OH	TYR	A	59	-13.721	-2.311	9.079

CCP4 v 7.0.0 (64-bit)

Figure 11K

ATOM	560	HH	TYR	A	59	-14.606	-2.771	9.154
ATOM	561	N	ASP	A	60	-14.151	6.542	9.300
ATOM	562	H	ASP	A	60	-14.954	6.464	8.709
ATOM	563	CA	ASP	A	60	-13.822	7.836	9.846
ATOM	564	C	ASP	A	60	-14.782	8.226	10.947
ATOM	565	O	ASP	A	60	-15.941	7.765	11.053
ATOM	566	CB	ASP	A	60	-13.861	8.942	8.769
ATOM	567	CG	ASP	A	60	-12.735	8.830	7.725
ATOM	568	OD1	ASP	A	60	-11.545	8.874	8.075
ATOM	569	OD2	ASP	A	60	-13.060	8.702	6.544
ATOM	570	N	GLN	A	61	-14.339	9.154	11.833
ATOM	571	H	GLN	A	61	-13.385	9.451	11.804
ATOM	572	CA	GLN	A	61	-15.151	9.804	12.885
ATOM	573	C	GLN	A	61	-15.839	8.803	13.802
ATOM	574	O	GLN	A	61	-17.008	8.893	14.229
ATOM	575	CB	GLN	A	61	-16.097	10.908	12.338
ATOM	576	CG	GLN	A	61	-16.239	12.133	13.262
ATOM	577	CD	GLN	A	61	-16.910	13.366	12.629
ATOM	578	OE1	GLN	A	61	-16.509	13.854	11.586
ATOM	579	NE2	GLN	A	61	-17.937	13.887	13.292
ATOM	580	1HE2	GLN	A	61	-18.416	14.689	12.934
ATOM	581	2HE2	GLN	A	61	-18.239	13.482	14.155
ATOM	582	N	ILE	A	62	-15.060	7.760	14.175
ATOM	583	H	ILE	A	62	-14.111	7.714	13.862
ATOM	584	CA	ILE	A	62	-15.557	6.705	15.015
ATOM	585	C	ILE	A	62	-15.251	7.057	16.447
ATOM	586	O	ILE	A	62	-14.198	7.613	16.837
ATOM	587	CB	ILE	A	62	-14.829	5.397	14.653
ATOM	588	CG1	ILE	A	62	-15.253	4.966	13.258
ATOM	589	CG2	ILE	A	62	-15.106	4.271	15.675
ATOM	590	CD1	ILE	A	62	-16.779	4.788	13.116
ATOM	591	N	LEU	A	63	-16.242	6.807	17.320
ATOM	592	H	LEU	A	63	-17.089	6.383	17.000
ATOM	593	CA	LEU	A	63	-16.127	7.131	18.719
ATOM	594	C	LEU	A	63	-15.518	5.942	19.425
ATOM	595	O	LEU	A	63	-15.869	4.753	19.269
ATOM	596	CB	LEU	A	63	-17.512	7.428	19.282
ATOM	597	CG	LEU	A	63	-17.660	7.598	20.813
ATOM	598	CD1	LEU	A	63	-16.711	8.632	21.404
ATOM	599	CD2	LEU	A	63	-19.089	7.963	21.201
ATOM	600	N	ILE	A	64	-14.511	6.211	20.219
ATOM	601	H	ILE	A	64	-14.185	7.153	20.305
ATOM	602	CA	ILE	A	64	-13.862	5.178	20.972
ATOM	603	C	ILE	A	64	-13.529	5.744	22.325
ATOM	604	O	ILE	A	64	-13.396	6.959	22.602
ATOM	605	CB	ILE	A	64	-12.618	4.716	20.231
ATOM	606	CG1	ILE	A	64	-11.925	3.573	20.949
ATOM	607	CG2	ILE	A	64	-11.690	5.865	19.950
ATOM	608	CD1	ILE	A	64	-10.905	2.888	20.062
ATOM	609	N	GLU	A	65	-13.396	4.815	23.294
ATOM	610	H	GLU	A	65	-13.443	3.844	23.059
ATOM	611	CA	GLU	A	65	-13.186	5.174	24.670
ATOM	612	C	GLU	A	65	-12.024	4.360	25.165
ATOM	613	O	GLU	A	65	-11.943	3.112	25.056
ATOM	614	CB	GLU	A	65	-14.459	4.823	25.405
ATOM	615	CG	GLU	A	65	-14.739	5.610	26.646

Figure 1L

ATOM	616	CD	GLU	A	65	-16.131	5.353	27.115
ATOM	617	OE1	GLU	A	65	-17.090	5.785	26.413
ATOM	618	OE2	GLU	A	65	-16.269	4.708	28.163
ATOM	619	N	ILE	A	66	-10.971	5.008	25.610
ATOM	620	H	ILE	A	66	-11.009	6.002	25.717
ATOM	621	CA	ILE	A	66	-9.762	4.317	25.947
ATOM	622	C	ILE	A	66	-9.571	4.586	27.413
ATOM	623	O	ILE	A	66	-9.422	5.732	27.880
ATOM	624	CB	ILE	A	66	-8.600	4.907	25.126
ATOM	625	CG1	ILE	A	66	-8.838	4.669	23.633
ATOM	626	CG2	ILE	A	66	-7.231	4.326	25.554
ATOM	627	CD1	ILE	A	66	-8.951	5.982	22.856
ATOM	628	N	CYS	A	67	-9.776	3.567	28.261
ATOM	629	H	CYS	A	67	-9.989	2.659	27.902
ATOM	630	CA	CYS	A	67	-9.698	3.740	29.687
ATOM	631	C	CYS	A	67	-10.673	4.871	30.088
ATOM	632	O	CYS	A	67	-10.393	5.716	30.958
ATOM	633	CB	CYS	A	67	-8.251	4.003	30.156
ATOM	634	SG	CYS	A	67	-7.170	2.529	30.217
ATOM	635	N	GLY	A	68	-11.877	4.947	29.499
ATOM	636	H	GLY	A	68	-12.125	4.286	28.791
ATOM	637	CA	GLY	A	68	-12.788	5.984	29.903
ATOM	638	C	GLY	A	68	-12.581	7.322	29.241
ATOM	639	O	GLY	A	68	-13.404	8.253	29.376
ATOM	640	N	HIS	A	69	-11.504	7.545	28.471
ATOM	641	H	HIS	A	69	-10.817	6.827	28.360
ATOM	642	CA	HIS	A	69	-11.305	8.800	27.793
ATOM	643	C	HIS	A	69	-11.838	8.679	26.399
ATOM	644	O	HIS	A	69	-11.516	7.742	25.630
ATOM	645	CB	HIS	A	69	-9.831	9.128	27.724
ATOM	646	CG	HIS	A	69	-9.276	9.286	29.081
ATOM	647	ND1	HIS	A	69	-9.317	10.484	29.778
ATOM	648	HD1	HIS	A	69	-9.688	11.347	29.436
ATOM	649	CD2	HIS	A	69	-8.723	8.352	29.912
ATOM	650	CE1	HIS	A	69	-8.783	10.254	30.947
ATOM	651	NE2	HIS	A	69	-8.405	8.990	31.091
ATOM	652	N	LYS	A	70	-12.768	9.561	25.973
ATOM	653	H	LYS	A	70	-13.084	10.284	26.588
ATOM	654	CA	LYS	A	70	-13.325	9.492	24.646
ATOM	655	C	LYS	A	70	-12.346	10.074	23.653
ATOM	656	O	LYS	A	70	-11.587	11.055	23.864
ATOM	657	CB	LYS	A	70	-14.645	10.285	24.536
ATOM	658	CG	LYS	A	70	-15.837	9.703	25.330
ATOM	659	CD	LYS	A	70	-17.105	10.593	25.286
ATOM	660	CE	LYS	A	70	-18.293	10.011	26.092
ATOM	661	NZ	LYS	A	70	-18.802	8.702	25.608
ATOM	662	1HZ	LYS	A	70	-19.563	8.406	26.185
ATOM	663	3HZ	LYS	A	70	-18.069	8.023	25.650
ATOM	664	2HZ	LYS	A	70	-19.116	8.795	24.663
ATOM	665	N	ALA	A	71	-12.323	9.485	22.446
ATOM	666	H	ALA	A	71	-12.813	8.625	22.305
ATOM	667	CA	ALA	A	71	-11.616	10.044	21.333
ATOM	668	C	ALA	A	71	-12.529	9.795	20.171
ATOM	669	O	ALA	A	71	-13.351	8.850	20.146
ATOM	670	CB	ALA	A	71	-10.292	9.358	21.143
ATOM	671	N	ILE	A	72	-12.559	10.685	19.149



Figure 11M

ATOM	672	H	ILE	A	72	-12.006	11.517	19.200
ATOM	673	CA	ILE	A	72	-13.376	10.474	17.963
ATOM	674	C	ILE	A	72	-12.480	10.662	16.771
ATOM	675	O	ILE	A	72	-11.858	11.720	16.550
ATOM	676	CB	ILE	A	72	-14.541	11.464	17.882
ATOM	677	CG1	ILE	A	72	-15.306	11.455	19.196
ATOM	678	CG2	ILE	A	72	-15.429	11.203	16.651
ATOM	679	CD1	ILE	A	72	-16.446	12.415	19.176
ATOM	680	N	GLY	A	73	-12.252	9.633	15.958
ATOM	681	H	GLY	A	73	-12.778	8.789	16.067
ATOM	682	CA	GLY	A	73	-11.253	9.755	14.938
ATOM	683	C	GLY	A	73	-11.283	8.554	14.034
ATOM	684	O	GLY	A	73	-12.211	7.706	14.006
ATOM	685	N	THR	A	74	-10.247	8.428	13.182
ATOM	686	H	THR	A	74	-9.471	9.055	13.250
ATOM	687	CA	THR	A	74	-10.201	7.416	12.158
ATOM	688	C	THR	A	74	-9.674	6.134	12.760
ATOM	689	O	THR	A	74	-8.670	6.034	13.497
ATOM	690	CB	THR	A	74	-9.298	7.895	11.048
ATOM	691	OG1	THR	A	74	-9.910	9.019	10.441
ATOM	692	HG1	THR	A	74	-9.335	9.362	9.698
ATOM	693	CG2	THR	A	74	-9.088	6.823	9.946
ATOM	694	N	VAL	A	75	-10.318	5.027	12.327
ATOM	695	H	VAL	A	75	-11.066	5.114	11.669
ATOM	696	CA	VAL	A	75	-9.968	3.717	12.778
ATOM	697	C	VAL	A	75	-9.906	2.843	11.551
ATOM	698	O	VAL	A	75	-10.803	2.807	10.681
ATOM	699	CB	VAL	A	75	-11.044	3.250	13.737
ATOM	700	CG1	VAL	A	75	-11.021	1.721	13.943
ATOM	701	CG2	VAL	A	75	-10.915	4.019	15.034
ATOM	702	N	LEU	A	76	-8.768	2.139	11.366
ATOM	703	H	LEU	A	76	-8.002	2.260	11.998
ATOM	704	CA	LEU	A	76	-8.566	1.183	10.276
ATOM	705	C	LEU	A	76	-8.848	-0.211	10.808
ATOM	706	O	LEU	A	76	-8.514	-0.582	11.958
ATOM	707	CB	LEU	A	76	-7.103	1.270	9.798
ATOM	708	CG	LEU	A	76	-6.608	2.684	9.443
ATOM	709	CD1	LEU	A	76	-5.151	2.645	9.087
ATOM	710	CD2	LEU	A	76	-7.396	3.302	8.296
ATOM	711	N	VAL	A	77	-9.569	-1.062	10.042
ATOM	712	H	VAL	A	77	-9.894	-0.766	9.144
ATOM	713	CA	VAL	A	77	-9.899	-2.428	10.485
ATOM	714	C	VAL	A	77	-9.298	-3.412	9.482
ATOM	715	O	VAL	A	77	-9.450	-3.300	8.253
ATOM	716	CB	VAL	A	77	-11.436	-2.592	10.506
ATOM	717	CG1	VAL	A	77	-11.830	-4.021	10.682
ATOM	718	CG2	VAL	A	77	-12.072	-1.765	11.634
ATOM	719	N	GLY	A	78	-8.560	-4.402	9.928
ATOM	720	H	GLY	A	78	-8.445	-4.530	10.913
ATOM	721	CA	GLY	A	78	-7.930	-5.285	8.987
ATOM	722	C	GLY	A	78	-7.228	-6.380	9.732
ATOM	723	O	GLY	A	78	-7.292	-6.524	10.970
ATOM	724	N	PRO	A	79	-6.512	-7.271	9.003
ATOM	725	CA	PRO	A	79	-5.880	-8.467	9.602
ATOM	726	C	PRO	A	79	-4.599	-8.107	10.340
ATOM	727	O	PRO	A	79	-3.449	-8.489	10.032

Figure 11N

ATOM	728	CB	PRO	A	79	-5.613	-9.379	8.400
ATOM	729	CG	PRO	A	79	-5.529	-8.416	7.210
ATOM	730	CD	PRO	A	79	-6.415	-7.225	7.537
ATOM	731	N	THR	A	80	-4.759	-7.304	11.408
ATOM	732	H	THR	A	80	-5.664	-6.935	11.619
ATOM	733	CA	THR	A	80	-3.658	-6.957	12.263
ATOM	734	C	THR	A	80	-3.490	-8.075	13.308
ATOM	735	O	THR	A	80	-4.447	-8.642	13.857
ATOM	736	CB	THR	A	80	-3.868	-5.572	12.927
ATOM	737	OG1	THR	A	80	-2.770	-5.303	13.78
ATOM	738	HG1	THR	A	80	-2.889	-4.412	14.225
ATOM	739	CG2	THR	A	80	-5.210	-5.464	13.678
ATOM	740	N	PRO	A	81	-2.243	-8.496	13.589
ATOM	741	CA	PRO	A	81	-1.986	-9.476	14.660
ATOM	742	C	PRO	A	81	-2.499	-8.952	16.001
ATOM	743	O	PRO	A	81	-2.944	-9.720	16.866
ATOM	744	CB	PRO	A	81	-0.444	-9.549	14.732
ATOM	745	CG	PRO	A	81	0.069	-8.951	13.429
ATOM	746	CD	PRO	A	81	-1.029	-8.105	12.842
ATOM	747	N	VAL	A	82	-2.474	-7.621	16.276
ATOM	748	H	VAL	A	82	-2.180	-6.975	15.571
ATOM	749	CA	VAL	A	82	-2.869	-7.091	17.591
ATOM	750	C	VAL	A	82	-3.605	-5.761	17.379
ATOM	751	O	VAL	A	82	-3.349	-5.004	16.429
ATOM	752	CB	VAL	A	82	-1.595	-6.858	18.443
ATOM	753	CG1	VAL	A	82	-0.650	-5.824	17.803
ATOM	754	CG2	VAL	A	82	-1.907	-6.418	19.890
ATOM	755	N	ASN	A	83	-4.548	-5.371	18.260
ATOM	756	H	ASN	A	83	-4.810	-5.981	19.007
ATOM	757	CA	ASN	A	83	-5.181	-4.067	18.123
ATOM	758	C	ASN	A	83	-4.195	-3.019	18.565
ATOM	759	O	ASN	A	83	-3.605	-3.064	19.665
ATOM	760	CB	ASN	A	83	-6.436	-3.942	18.982
ATOM	761	CG	ASN	A	83	-7.502	-4.930	18.631
ATOM	762	OD1	ASN	A	83	-7.899	-5.049	17.488
ATOM	763	ND2	ASN	A	83	-7.980	-5.662	19.628
ATOM	764	2HD2	ASN	A	83	-8.695	-6.341	19.459
ATOM	765	1HD2	ASN	A	83	-7.630	-5.541	20.557
ATOM	766	N	ILE	A	84	-4.007	-1.951	17.770
ATOM	767	H	ILE	A	84	-4.583	-1.827	16.962
ATOM	768	CA	ILE	A	84	-2.993	-0.954	18.032
ATOM	769	C	ILE	A	84	-3.679	0.387	18.114
ATOM	770	O	ILE	A	84	-4.460	0.797	17.240
ATOM	771	CB	ILE	A	84	-2.021	-0.922	16.833
ATOM	772	CG1	ILE	A	84	-1.162	-2.150	16.859
ATOM	773	CG2	ILE	A	84	-1.219	0.387	16.747
ATOM	774	CD1	ILE	A	84	-0.375	-2.360	15.579
ATOM	775	N	ILE	A	85	-3.471	1.155	19.203
ATOM	776	H	ILE	A	85	-2.972	0.781	19.985
ATOM	777	CA	ILE	A	85	-3.951	2.518	19.281
ATOM	778	C	ILE	A	85	-2.784	3.425	18.949
ATOM	779	O	ILE	A	85	-1.767	3.515	19.663
ATOM	780	CB	ILE	A	85	-4.522	2.825	20.676
ATOM	781	CG1	ILE	A	85	-5.673	1.865	21.050
ATOM	782	CG2	ILE	A	85	-5.000	4.274	20.716
ATOM	783	CD1	ILE	A	85	-6.828	1.808	20.059

Figure 110

ATOM	784	N	GLY	A	86	-2.820	4.123	17.792
ATOM	785	H	GLY	A	86	-3.637	4.087	17.217
ATOM	786	CA	GLY	A	86	-1.690	4.936	17.351
ATOM	787	C	GLY	A	86	-1.831	6.393	17.704
ATOM	788	O	GLY	A	86	-2.760	6.864	18.390
ATOM	789	N	ARG	A	87	-0.881	7.229	17.230
ATOM	790	H	ARG	A	87	-0.204	6.890	16.577
ATOM	791	CA	ARG	A	87	-0.810	8.623	17.643
ATOM	792	C	ARG	A	87	-2.027	9.445	17.277
ATOM	793	O	ARG	A	87	-2.365	10.430	17.963
ATOM	794	CB	ARG	A	87	0.450	9.275	17.057
ATOM	795	CG	ARG	A	87	1.735	8.496	17.205
ATOM	796	CD	ARG	A	87	2.762	8.916	16.207
ATOM	797	NE	ARG	A	87	3.875	7.961	16.117
ATOM	798	HE	ARG	A	87	4.035	7.353	16.895
ATOM	799	CZ	ARG	A	87	4.660	7.893	15.035
ATOM	800	NH1	ARG	A	87	4.463	8.675	13.975
ATOM	801	2HH1	ARG	A	87	3.712	9.335	13.974
ATOM	802	1HH1	ARG	A	87	5.066	8.602	13.181
ATOM	803	NH2	ARG	A	87	5.656	7.019	15.023
ATOM	804	1HH2	ARG	A	87	6.254	6.953	14.224
ATOM	805	2HH2	ARG	A	87	5.810	6.426	15.813
ATOM	806	N	ASN	A	88	-2.780	9.120	16.214
ATOM	807	H	ASN	A	88	-2.504	8.361	15.625
ATOM	808	CA	ASN	A	88	-4.015	9.860	15.890
ATOM	809	C	ASN	A	88	-4.963	9.921	17.069
ATOM	810	O	ASN	A	88	-5.613	10.954	17.345
ATOM	811	CB	ASN	A	88	-4.712	9.315	14.617
ATOM	812	CG	ASN	A	88	-5.475	8.001	14.827
ATOM	813	OD1	ASN	A	88	-4.922	6.996	15.245
ATOM	814	ND2	ASN	A	88	-6.758	7.998	14.506
ATOM	815	2HD2	ASN	A	88	-7.306	7.169	14.622
ATOM	816	1HD2	ASN	A	88	-7.190	8.824	14.145
ATOM	817	N	LEU	A	89	-5.130	8.847	17.848
ATOM	818	H	LEU	A	89	-4.637	8.002	17.640
ATOM	819	CA	LEU	A	89	-6.024	8.865	19.013
ATOM	820	C	LEU	A	89	-5.275	9.091	20.309
ATOM	821	O	LEU	A	89	-5.834	9.632	21.283
ATOM	822	CB	LEU	A	89	-6.840	7.592	19.140
ATOM	823	CG	LEU	A	89	-7.759	7.355	17.957
ATOM	824	CD1	LEU	A	89	-8.369	5.980	18.088
ATOM	825	CD2	LEU	A	89	-8.817	8.457	17.801
ATOM	826	N	LEU	A	90	-3.983	8.745	20.428
ATOM	827	H	LEU	A	90	-3.525	8.274	19.674
ATOM	828	CA	LEU	A	90	-3.242	9.057	21.664
ATOM	829	C	LEU	A	90	-3.155	10.555	21.932
ATOM	830	O	LEU	A	90	-3.202	11.020	23.092
ATOM	831	CB	LEU	A	90	-1.817	8.453	21.661
ATOM	832	CG	LEU	A	90	-1.766	6.914	21.587
ATOM	833	CD1	LEU	A	90	-0.343	6.494	21.396
ATOM	834	CD2	LEU	A	90	-2.339	6.230	22.812
ATOM	835	N	THR	A	91	-3.031	11.407	20.926
ATOM	836	H	THR	A	91	-2.982	11.063	19.988
ATOM	837	CA	THR	A	91	-2.964	12.834	21.155
ATOM	838	C	THR	A	91	-4.309	13.331	21.635
ATOM	839	O	THR	A	91	-4.422	14.315	22.398

Figure 11p

ATOM	840	CB	THR	A	91	-2.555	13.543	19.848
ATOM	841	OG1	THR	A	91	-3.459	13.214	18.802
ATOM	842	HG1	THR	A	91	-3.188	13.677	17.958
ATOM	843	CG2	THR	A	91	-1.153	13.122	19.395
ATOM	844	N	GLN	A	92	-5.435	12.704	21.258
ATOM	845	H	GLN	A	92	-5.379	11.892	20.677
ATOM	846	CA	GLN	A	92	-6.763	13.186	21.682
ATOM	847	C	GLN	A	92	-6.942	12.975	23.153
ATOM	848	O	GLN	A	92	-7.554	13.797	23.871
ATOM	849	CB	GLN	A	92	-7.890	12.479	20.964
ATOM	850	CG	GLN	A	92	-7.937	12.862	19.517
ATOM	851	CD	GLN	A	92	-9.251	12.515	18.886
ATOM	852	OE1	GLN	A	92	-10.270	12.424	19.546
ATOM	853	NE2	GLN	A	92	-9.202	12.323	17.588
ATOM	854	1HE2	GLN	A	92	-10.031	12.087	17.080
ATOM	855	2HE2	GLN	A	92	-8.336	12.411	17.097
ATOM	856	N	ILE	A	93	-6.472	11.846	23.721
ATOM	857	H	ILE	A	93	-6.014	11.160	23.155
ATOM	858	CA	ILE	A	93	-6.608	11.578	25.165
ATOM	859	C	ILE	A	93	-5.472	12.189	25.948
ATOM	860	O	ILE	A	93	-5.342	12.031	27.171
ATOM	861	CB	ILE	A	93	-6.820	10.073	25.484
ATOM	862	CG1	ILE	A	93	-5.536	9.221	25.286
ATOM	863	CG2	ILE	A	93	-8.022	9.486	24.735
ATOM	864	CD1	ILE	A	93	-5.754	7.740	25.693
ATOM	865	N	GLY	A	94	-4.594	12.993	25.330
ATOM	866	H	GLY	A	94	-4.617	13.079	24.334
ATOM	867	CA	GLY	A	94	-3.613	13.742	26.063
ATOM	868	C	GLY	A	94	-2.448	12.895	26.512
ATOM	869	O	GLY	A	94	-1.764	13.158	27.519
ATOM	870	N	CYS	A	95	-2.117	11.849	25.797
ATOM	871	H	CYS	A	95	-2.619	11.644	24.957
ATOM	872	CA	CYS	A	95	-1.036	10.994	26.214
ATOM	873	C	CYS	A	95	0.362	11.566	25.925
ATOM	874	O	CYS	A	95	0.588	12.254	24.907
ATOM	875	CB	CYS	A	95	-1.260	9.655	25.550
ATOM	876	SG	CYS	A	95	-0.254	8.307	26.125
ATOM	877	N	THR	A	96	1.346	11.297	26.803
ATOM	878	H	THR	A	96	1.135	10.738	27.618
ATOM	879	CA	THR	A	96	2.728	11.779	26.664
ATOM	880	C	THR	A	96	3.729	10.784	27.264
ATOM	881	O	THR	A	96	3.498	10.249	28.345
ATOM	882	CB	THR	A	96	2.925	13.154	27.346
ATOM	883	OG1	THR	A	96	2.594	13.109	28.721
ATOM	884	HG1	THR	A	96	2.784	13.966	29.109
ATOM	885	CG2	THR	A	96	2.139	14.300	26.698
ATOM	886	N	LEU	A	97	4.882	10.603	26.599
ATOM	887	H	LEU	A	97	5.016	11.071	25.714
ATOM	888	CA	LEU	A	97	6.040	9.910	27.166
ATOM	889	C	LEU	A	97	6.751	10.824	28.175
ATOM	890	O	LEU	A	97	6.705	12.046	28.044
ATOM	891	CB	LEU	A	97	7.013	9.497	26.049
ATOM	892	CG	LEU	A	97	6.452	8.449	25.065
ATOM	893	CD1	LEU	A	97	7.360	8.355	23.828
ATOM	894	CD2	LEU	A	97	6.345	7.065	25.724
ATOM	895	N	ASN	A	98	7.412	10.221	29.175

00000000000000000000

Figure 11Q

ATOM	896	H	ASN	A	98	7.413	9.212	29.205
ATOM	897	CA	ASN	A	98	8.065	10.897	30.292
ATOM	898	C	ASN	A	98	9.220	10.029	30.800
ATOM	899	O	ASN	A	98	8.995	9.079	31.550
ATOM	900	CB	ASN	A	98	7.057	11.177	31.423
ATOM	901	CG	ASN	A	98	6.084	12.305	31.083
ATOM	902	OD1	ASN	A	98	4.983	12.062	30.594
ATOM	903	ND2	ASN	A	98	6.493	13.549	31.342
ATOM	904	2HD2	ASN	A	98	5.888	14.331	31.136
ATOM	905	1HD2	ASN	A	98	7.406	13.707	31.742
ATOM	906	N	LEU	A	99	10.451	10.369	30.389
ATOM	907	H	LEU	A	99	10.547	11.177	29.792
ATOM	908	CA	LEU	A	99	11.679	9.620	30.666
ATOM	909	C	LEU	A	99	12.711	10.437	31.454
ATOM	910	O	LEU	A	99	12.487	11.652	31.651
ATOM	911	CB	LEU	A	99	12.233	8.989	29.369
ATOM	912	CG	LEU	A	99	12.833	9.873	28.248
ATOM	913	CD1	LEU	A	99	11.876	10.947	27.705
ATOM	914	CD2	LEU	A	99	14.183	10.505	28.623
ATOM	915	OXT	LEU	A	99	13.716	9.819	31.869
TER								
ATOM	916	N	PRO	B	1	12.600	14.237	30.106
ATOM	917	CA	PRO	B	1	11.842	15.268	29.363
ATOM	918	C	PRO	B	1	10.430	14.773	29.138
ATOM	919	O	PRO	B	1	10.054	13.695	29.618
ATOM	920	CB	PRO	B	1	12.622	15.412	28.035
ATOM	921	CG	PRO	B	1	13.817	14.470	28.131
ATOM	922	CD	PRO	B	1	13.966	14.227	29.603
ATOM	923	1H	PRO	B	1	12.175	13.343	29.964
ATOM	924	2H	PRO	B	1	12.594	14.457	31.081
ATOM	925	N	GLN	B	2	9.513	15.542	28.523
ATOM	926	H	GLN	B	2	9.751	16.474	28.251
ATOM	927	CA	GLN	B	2	8.186	15.058	28.242
ATOM	928	C	GLN	B	2	8.066	15.151	26.749
ATOM	929	O	GLN	B	2	8.523	16.140	26.133
ATOM	930	CB	GLN	B	2	7.155	15.976	28.856
ATOM	931	CG	GLN	B	2	5.739	15.732	28.373
ATOM	932	CD	GLN	B	2	4.744	16.365	29.284
ATOM	933	OE1	GLN	B	2	4.628	15.962	30.431
ATOM	934	NE2	GLN	B	2	4.024	17.367	28.784
ATOM	935	1HE2	GLN	B	2	3.341	17.830	29.349
ATOM	936	2HE2	GLN	B	2	4.160	17.665	27.839
ATOM	937	N	ILE	B	3	7.499	14.176	26.036
ATOM	938	H	ILE	B	3	7.102	13.386	26.504
ATOM	939	CA	ILE	B	3	7.435	14.216	24.601
ATOM	940	C	ILE	B	3	5.956	14.097	24.184
ATOM	941	O	ILE	B	3	5.150	13.290	24.710
ATOM	942	CB	ILE	B	3	8.299	13.058	24.029
ATOM	943	CG1	ILE	B	3	9.743	13.232	24.534
ATOM	944	CG2	ILE	B	3	8.269	12.985	22.496
ATOM	945	CD1	ILE	B	3	10.621	12.068	24.143
ATOM	946	N	THR	B	4	5.462	15.108	23.453
ATOM	947	H	THR	B	4	6.046	15.887	23.226
ATOM	948	CA	THR	B	4	4.107	15.115	22.976
ATOM	949	C	THR	B	4	4.039	14.193	21.765
ATOM	950	O	THR	B	4	5.066	13.755	21.203

Figure 11R

ATOM	951	CB	THR	B	4	3.616	16.548	22.647
ATOM	952	OG1	THR	B	4	4.450	17.157	21.645
ATOM	953	HG1	THR	B	4	4.123	18.080	21.442
ATOM	954	CG2	THR	B	4	3.644	17.454	23.876
ATOM	955	N	LEU	B	5	2.872	13.781	21.324
ATOM	956	H	LEU	B	5	2.033	14.151	21.723
ATOM	957	CA	LEU	B	5	2.837	12.795	20.265
ATOM	958	C	LEU	B	5	2.183	13.415	19.047
ATOM	959	O	LEU	B	5	1.677	12.720	18.142
ATOM	960	CB	LEU	B	5	2.093	11.577	20.762
ATOM	961	CG	LEU	B	5	2.819	10.856	21.892
ATOM	962	CD1	LEU	B	5	1.889	9.885	22.602
ATOM	963	CD2	LEU	B	5	4.108	10.159	21.416
ATOM	964	N	TRP	B	6	2.209	14.742	18.880
ATOM	965	H	TRP	B	6	2.601	15.323	19.593
ATOM	966	CA	TRP	B	6	1.683	15.364	17.690
ATOM	967	C	TRP	B	6	2.581	14.978	16.509
ATOM	968	O	TRP	B	6	2.159	14.851	15.349
ATOM	969	CB	TRP	B	6	1.587	16.879	17.833
ATOM	970	CG	TRP	B	6	0.652	17.339	18.921
ATOM	971	CD1	TRP	B	6	0.955	17.584	20.232
ATOM	972	CD2	TRP	B	6	-0.750	17.612	18.783
ATOM	973	NE1	TRP	B	6	-0.167	17.989	20.913
ATOM	974	HE1	TRP	B	6	-0.217	18.230	21.882
ATOM	975	CE2	TRP	B	6	-1.224	18.013	20.048
ATOM	976	CE3	TRP	B	6	-1.637	17.550	17.709
ATOM	977	CZ2	TRP	B	6	-2.544	18.352	20.266
ATOM	978	CZ3	TRP	B	6	-2.947	17.885	17.921
ATOM	979	CH2	TRP	B	6	-3.394	18.281	19.185
ATOM	980	N	GLN	B	7	3.896	14.809	16.738
ATOM	981	H	GLN	B	7	4.267	14.985	17.650
ATOM	982	CA	GLN	B	7	4.794	14.376	15.689
ATOM	983	C	GLN	B	7	5.361	13.043	16.096
ATOM	984	O	GLN	B	7	5.221	12.586	17.243
ATOM	985	CB	GLN	B	7	5.880	15.430	15.505
ATOM	986	CG	GLN	B	7	5.353	16.704	14.804
ATOM	987	CD	GLN	B	7	6.197	17.912	15.137
ATOM	988	OE1	GLN	B	7	7.400	17.802	15.404
ATOM	989	NE2	GLN	B	7	5.553	19.083	15.121
ATOM	990	1HE2	GLN	B	7	6.040	19.931	15.330
ATOM	991	2HE2	GLN	B	7	4.579	19.121	14.900
ATOM	992	N	ARG	B	8	5.979	12.274	15.189
ATOM	993	H	ARG	B	8	6.073	12.597	14.247
ATOM	994	CA	ARG	B	8	6.505	10.985	15.573
ATOM	995	C	ARG	B	8	7.577	11.198	16.610
ATOM	996	O	ARG	B	8	8.395	12.130	16.515
ATOM	997	CB	ARG	B	8	7.092	10.238	14.384
ATOM	998	CG	ARG	B	8	6.132	10.018	13.237
ATOM	999	CD	ARG	B	8	6.802	9.402	12.046
ATOM	1000	NE	ARG	B	8	5.846	9.005	11.023
ATOM	1001	HE	ARG	B	8	4.872	9.080	11.237
ATOM	1002	CZ	ARG	B	8	6.217	8.552	9.828
ATOM	1003	NH1	ARG	B	8	7.496	8.442	9.486
ATOM	1004	2HH1	ARG	B	8	8.211	8.703	10.134
ATOM	1005	1HH1	ARG	B	8	7.744	8.098	8.580
ATOM	1006	NH2	ARG	B	8	5.279	8.202	8.952

Figure 11g

ATOM	1007	1HH2	ARG	B	8	5.540	7.860	8.050
ATOM	1008	2HH2	ARG	B	8	4.312	8.281	9.196
ATOM	1009	N	PRO	B	9	7.663	10.381	17.682
ATOM	1010	CA	PRO	B	9	8.666	10.587	18.746
ATOM	1011	C	PRO	B	9	10.065	10.196	18.315
ATOM	1012	O	PRO	B	9	10.678	9.215	18.778
ATOM	1013	CB	PRO	B	9	8.148	9.682	19.878
ATOM	1014	CG	PRO	B	9	7.315	8.607	19.206
ATOM	1015	CD	PRO	B	9	6.708	9.323	18.004
ATOM	1016	N	LEU	B	10	10.685	10.969	17.400
ATOM	1017	H	LEU	B	10	10.201	11.746	16.998
ATOM	1018	CA	LEU	B	10	12.040	10.706	16.978
ATOM	1019	C	LEU	B	10	12.976	11.498	17.850
ATOM	1020	O	LEU	B	10	12.880	12.733	18.018
ATOM	1021	CB	LEU	B	10	12.250	11.170	15.554
ATOM	1022	CG	LEU	B	10	11.427	10.386	14.551
ATOM	1023	CD1	LEU	B	10	11.385	11.175	13.276
ATOM	1024	CD2	LEU	B	10	11.956	8.947	14.355
ATOM	1025	N	VAL	B	11	14.030	10.843	18.384
ATOM	1026	H	VAL	B	11	14.148	9.866	18.206
ATOM	1027	CA	VAL	B	11	15.018	11.517	19.223
ATOM	1028	C	VAL	B	11	16.400	11.111	18.740
ATOM	1029	O	VAL	B	11	16.581	10.201	17.911
ATOM	1030	CB	VAL	B	11	14.857	11.100	20.699
ATOM	1031	CG1	VAL	B	11	13.514	11.586	21.293
ATOM	1032	CG2	VAL	B	11	15.038	9.573	20.903
ATOM	1033	N	THR	B	12	17.485	11.739	19.232
ATOM	1034	H	THR	B	12	17.370	12.507	19.862
ATOM	1035	CA	THR	B	12	18.843	11.325	18.868
ATOM	1036	C	THR	B	12	19.377	10.284	19.837
ATOM	1037	O	THR	B	12	19.237	10.352	21.082
ATOM	1038	CB	THR	B	12	19.830	12.520	18.820
ATOM	1039	OG1	THR	B	12	19.389	13.483	17.876
ATOM	1040	HG1	THR	B	12	20.028	14.252	17.848
ATOM	1041	CG2	THR	B	12	21.234	12.075	18.399
ATOM	1042	N	ILE	B	13	20.044	9.234	19.338
ATOM	1043	H	ILE	B	13	20.135	9.130	18.348
ATOM	1044	CA	ILE	B	13	20.641	8.239	20.176
ATOM	1045	C	ILE	B	13	22.119	8.226	19.855
ATOM	1046	O	ILE	B	13	22.579	8.817	18.865
ATOM	1047	CB	ILE	B	13	19.993	6.870	19.879
ATOM	1048	CG1	ILE	B	13	20.192	6.464	18.415
ATOM	1049	CG2	ILE	B	13	18.482	6.893	20.206
ATOM	1050	CD1	ILE	B	13	19.829	5.035	18.106
ATOM	1051	N	LYS	B	14	22.973	7.618	20.661
ATOM	1052	H	LYS	B	14	22.652	7.243	21.531
ATOM	1053	CA	LYS	B	14	24.364	7.480	20.317
ATOM	1054	C	LYS	B	14	24.680	6.029	20.477
ATOM	1055	O	LYS	B	14	24.353	5.353	21.484
ATOM	1056	CB	LYS	B	14	25.266	8.263	21.242
ATOM	1057	CG	LYS	B	14	24.947	9.729	21.236
ATOM	1058	CD	LYS	B	14	25.664	10.498	22.339
ATOM	1059	CE	LYS	B	14	26.758	11.441	21.807
ATOM	1060	NZ	LYS	B	14	28.026	10.781	21.440
ATOM	1061	1HZ	LYS	B	14	28.674	11.466	21.107
ATOM	1062	3HZ	LYS	B	14	27.855	10.107	20.722

Figure 11T

ATOM	1063	2HZ	LYS	B	14	28.408	10.323	22.243
ATOM	1064	N	ILE	B	15	25.214	5.390	19.425
ATOM	1065	H	ILE	B	15	25.434	5.901	18.594
ATOM	1066	CA	ILE	B	15	25.489	3.989	19.434
ATOM	1067	C	ILE	B	15	26.832	3.981	18.750
ATOM	1068	O	ILE	B	15	27.104	4.869	17.933
ATOM	1069	CB	ILE	B	15	24.435	3.220	18.606
ATOM	1070	CG1	ILE	B	15	24.893	1.824	18.347
ATOM	1071	CG2	ILE	B	15	24.048	3.977	17.309
ATOM	1072	CD1	ILE	B	15	23.830	0.996	17.645
ATOM	1073	N	GLY	B	16	27.812	3.212	19.202
ATOM	1074	H	GLY	B	16	27.623	2.535	19.913
ATOM	1075	CA	GLY	B	16	29.175	3.336	18.677
ATOM	1076	C	GLY	B	16	29.771	4.754	18.619
ATOM	1077	O	GLY	B	16	30.737	4.970	17.902
ATOM	1078	N	GLY	B	17	29.273	5.791	19.335
ATOM	1079	H	GLY	B	17	28.453	5.660	19.892
ATOM	1080	CA	GLY	B	17	29.924	7.105	19.302
ATOM	1081	C	GLY	B	17	29.468	8.043	18.176
ATOM	1082	O	GLY	B	17	29.984	9.155	17.933
ATOM	1083	N	GLN	B	18	28.433	7.621	17.411
ATOM	1084	H	GLN	B	18	28.046	6.711	17.560
ATOM	1085	CA	GLN	B	18	27.834	8.449	16.348
ATOM	1086	C	GLN	B	18	26.407	8.755	16.736
ATOM	1087	O	GLN	B	18	25.678	7.953	17.353
ATOM	1088	CB	GLN	B	18	27.810	7.645	15.045
ATOM	1089	CG	GLN	B	18	27.247	6.204	15.146
ATOM	1090	CD	GLN	B	18	27.572	5.333	13.924
ATOM	1091	OE1	GLN	B	18	26.771	4.501	13.464
ATOM	1092	NE2	GLN	B	18	28.766	5.531	13.393
ATOM	1093	1HE2	GLN	B	18	29.057	5.005	12.594
ATOM	1094	2HE2	GLN	B	18	29.388	6.209	13.786
ATOM	1095	N	LEU	B	19	25.873	9.933	16.337
ATOM	1096	H	LEU	B	19	26.446	10.602	15.863
ATOM	1097	CA	LEU	B	19	24.467	10.267	16.578
ATOM	1098	C	LEU	B	19	23.633	9.622	15.490
ATOM	1099	O	LEU	B	19	23.912	9.707	14.284
ATOM	1100	CB	LEU	B	19	24.207	11.777	16.457
ATOM	1101	CG	LEU	B	19	24.857	12.756	17.454
ATOM	1102	CD1	LEU	B	19	24.739	12.335	18.880
ATOM	1103	CD2	LEU	B	19	26.299	13.072	17.130
ATOM	1104	N	LYS	B	20	22.450	9.085	15.850
ATOM	1105	H	LYS	B	20	22.242	8.948	16.819
ATOM	1106	CA	LYS	B	20	21.472	8.702	14.867
ATOM	1107	C	LYS	B	20	20.121	9.105	15.417
ATOM	1108	O	LYS	B	20	19.957	9.572	16.569
ATOM	1109	CB	LYS	B	20	21.496	7.200	14.560
ATOM	1110	CG	LYS	B	20	22.904	6.653	14.507
ATOM	1111	CD	LYS	B	20	23.052	5.366	13.677
ATOM	1112	CE	LYS	B	20	23.069	5.603	12.145
ATOM	1113	NZ	LYS	B	20	23.893	6.758	11.699
ATOM	1114	1HZ	LYS	B	20	23.847	6.836	10.703
ATOM	1115	3HZ	LYS	B	20	24.843	6.617	11.978
ATOM	1116	2HZ	LYS	B	20	23.544	7.597	12.116
ATOM	1117	N	GLU	B	21	19.068	9.022	14.591
ATOM	1118	H	GLU	B	21	19.200	8.712	13.650



Figure 11U

ATOM	1119	CA	GLU	B	21	17.735	9.366	15.008
ATOM	1120	C	GLU	B	21	16.937	8.095	15.119
ATOM	1121	O	GLU	B	21	17.117	7.103	14.376
ATOM	1122	CB	GLU	B	21	17.143	10.314	13.983
ATOM	1123	CG	GLU	B	21	15.714	10.706	14.162
ATOM	1124	CD	GLU	B	21	15.304	11.607	13.036
ATOM	1125	OE1	GLU	B	21	14.971	11.051	11.957
ATOM	1126	OE2	GLU	B	21	15.338	12.854	13.174
ATOM	1127	N	ALA	B	22	16.025	7.999	16.072
ATOM	1128	H	ALA	B	22	15.825	8.792	16.648
ATOM	1129	CA	ALA	B	22	15.300	6.783	16.315
ATOM	1130	C	ALA	B	22	13.981	7.132	16.952
ATOM	1131	O	ALA	B	22	13.756	8.153	17.632
ATOM	1132	CB	ALA	B	22	16.095	5.865	17.235
ATOM	1133	N	LEU	B	23	12.994	6.230	16.743
ATOM	1134	H	LEU	B	23	13.195	5.379	16.257
ATOM	1135	CA	LEU	B	23	11.639	6.408	17.180
ATOM	1136	C	LEU	B	23	11.476	5.740	18.534
ATOM	1137	O	LEU	B	23	11.814	4.564	18.746
ATOM	1138	CB	LEU	B	23	10.775	5.665	16.192
ATOM	1139	CG	LEU	B	23	9.267	5.810	16.237
ATOM	1140	CD1	LEU	B	23	8.807	7.142	15.664
ATOM	1141	CD2	LEU	B	23	8.648	4.625	15.482
ATOM	1142	N	LEU	B	24	10.948	6.455	19.553
ATOM	1143	H	LEU	B	24	10.775	7.433	19.435
ATOM	1144	CA	LEU	B	24	10.613	5.838	20.849
ATOM	1145	C	LEU	B	24	9.271	5.160	20.687
ATOM	1146	O	LEU	B	24	8.208	5.764	20.418
ATOM	1147	CB	LEU	B	24	10.564	6.878	21.971
ATOM	1148	CG	LEU	B	24	11.828	7.750	22.075
ATOM	1149	CD1	LEU	B	24	11.580	8.859	23.077
ATOM	1150	CD2	LEU	B	24	13.099	6.955	22.388
ATOM	1151	N	ASP	B	25	9.246	3.822	20.809
ATOM	1152	H	ASP	B	25	10.025	3.347	21.218
ATOM	1153	CA	ASP	B	25	8.122	3.030	20.366
ATOM	1154	C	ASP	B	25	7.637	2.136	21.484
ATOM	1155	O	ASP	B	25	8.189	1.048	21.759
ATOM	1156	CB	ASP	B	25	8.613	2.196	19.189
ATOM	1157	CG	ASP	B	25	7.528	1.421	18.511
ATOM	1158	OD1	ASP	B	25	6.422	1.339	19.058
ATOM	1159	OD2	ASP	B	25	7.800	0.897	17.426
ATOM	1160	N	THR	B	26	6.547	2.465	22.157
ATOM	1161	H	THR	B	26	6.067	3.314	21.938
ATOM	1162	CA	THR	B	26	6.025	1.621	23.212
ATOM	1163	C	THR	B	26	5.347	0.369	22.694
ATOM	1164	O	THR	B	26	4.976	-0.550	23.451
ATOM	1165	CB	THR	B	26	5.027	2.389	24.046
ATOM	1166	OG1	THR	B	26	3.927	2.853	23.239
ATOM	1167	HG1	THR	B	26	3.277	3.359	23.806
ATOM	1168	CG2	THR	B	26	5.703	3.603	24.650
ATOM	1169	N	GLY	B	27	5.090	0.245	21.382
ATOM	1170	H	GLY	B	27	5.341	0.983	20.756
ATOM	1171	CA	GLY	B	27	4.457	-0.938	20.867
ATOM	1172	C	GLY	B	27	5.475	-1.992	20.458
ATOM	1173	O	GLY	B	27	5.121	-3.108	20.055
ATOM	1174	N	ALA	B	28	6.792	-1.717	20.495

Figure 11v

ATOM	1175	H	ALA	B	28	7.104	-0.832	20.841
ATOM	1176	CA	ALA	B	28	7.800	-2.690	20.037
ATOM	1177	C	ALA	B	28	8.371	-3.444	21.259
ATOM	1178	O	ALA	B	28	8.840	-2.807	22.213
ATOM	1179	CB	ALA	B	28	8.924	-1.936	19.358
ATOM	1180	N	ASP	B	29	8.459	-4.787	21.289
ATOM	1181	H	ASP	B	29	8.082	-5.325	20.535
ATOM	1182	CA	ASP	B	29	9.121	-5.441	22.452
ATOM	1183	C	ASP	B	29	10.608	-5.219	22.404
ATOM	1184	O	ASP	B	29	11.345	-5.264	23.412
ATOM	1185	CB	ASP	B	29	8.965	-6.975	22.447
ATOM	1186	CG	ASP	B	29	7.551	-7.477	22.774
ATOM	1187	OD1	ASP	B	29	6.683	-6.693	23.169
ATOM	1188	OD2	ASP	B	29	7.350	-8.686	22.616
ATOM	1189	N	ASP	B	30	11.164	-5.157	21.171
ATOM	1190	H	ASP	B	30	10.577	-5.063	20.367
ATOM	1191	CA	ASP	B	30	12.609	-5.217	20.880
ATOM	1192	C	ASP	B	30	13.048	-3.886	20.335
ATOM	1193	O	ASP	B	30	12.269	-3.055	19.817
ATOM	1194	CB	ASP	B	30	12.833	-6.226	19.735
ATOM	1195	CG	ASP	B	30	12.477	-7.675	20.099
ATOM	1196	OD1	ASP	B	30	13.197	-8.272	20.908
ATOM	1197	OD2	ASP	B	30	11.494	-8.237	19.569
ATOM	1198	N	THR	B	31	14.387	-3.692	20.227
ATOM	1199	H	THR	B	31	15.018	-4.380	20.586
ATOM	1200	CA	THR	B	31	14.981	-2.530	19.614
ATOM	1201	C	THR	B	31	15.578	-2.979	18.260
ATOM	1202	O	THR	B	31	16.246	-4.020	18.123
ATOM	1203	CB	THR	B	31	16.036	-2.004	20.557
ATOM	1204	OG1	THR	B	31	15.378	-1.376	21.645
ATOM	1205	HG1	THR	B	31	16.052	-1.016	22.290
ATOM	1206	CG2	THR	B	31	16.944	-0.960	19.904
ATOM	1207	N	VAL	B	32	15.237	-2.283	17.150
ATOM	1208	H	VAL	B	32	14.703	-1.442	17.237
ATOM	1209	CA	VAL	B	32	15.626	-2.722	15.806
ATOM	1210	C	VAL	B	32	16.303	-1.566	15.132
ATOM	1211	O	VAL	B	32	15.779	-0.428	14.995
ATOM	1212	CB	VAL	B	32	14.407	-3.126	14.964
ATOM	1213	CG1	VAL	B	32	14.820	-3.703	13.596
ATOM	1214	CG2	VAL	B	32	13.556	-4.102	15.703
ATOM	1215	N	LEU	B	33	17.563	-1.756	14.720
ATOM	1216	H	LEU	B	33	17.984	-2.658	14.814
ATOM	1217	CA	LEU	B	33	18.347	-0.697	14.138
ATOM	1218	C	LEU	B	33	18.610	-1.009	12.685
ATOM	1219	O	LEU	B	33	18.685	-2.162	12.205
ATOM	1220	CB	LEU	B	33	19.679	-0.628	14.856
ATOM	1221	CG	LEU	B	33	19.698	0.363	16.031
ATOM	1222	CD1	LEU	B	33	18.425	0.321	16.891
ATOM	1223	CD2	LEU	B	33	20.929	0.179	16.889
ATOM	1224	N	GLU	B	34	18.786	0.078	11.899
ATOM	1225	H	GLU	B	34	18.619	0.991	12.271
ATOM	1226	CA	GLU	B	34	19.218	0.041	10.488
ATOM	1227	C	GLU	B	34	20.478	-0.774	10.399
ATOM	1228	O	GLU	B	34	21.374	-0.835	11.272
ATOM	1229	CB	GLU	B	34	19.536	1.460	9.996
ATOM	1230	CG	GLU	B	34	20.722	2.088	10.761

Figure 11W

ATOM	1231	CD	GLU	B	34	21.085	3.512	10.314
ATOM	1232	OE1	GLU	B	34	20.285	4.466	10.500
ATOM	1233	OE2	GLU	B	34	22.211	3.703	9.775
ATOM	1234	N	GLU	B	35	20.673	-1.367	9.205
ATOM	1235	H	GLU	B	35	20.011	-1.227	8.468
ATOM	1236	CA	GLU	B	35	21.802	-2.205	8.930
ATOM	1237	C	GLU	B	35	23.096	-1.520	9.321
ATOM	1238	O	GLU	B	35	23.391	-0.379	8.916
ATOM	1239	CB	GLU	B	35	21.741	-2.479	7.439
ATOM	1240	CG	GLU	B	35	22.795	-3.380	6.883
ATOM	1241	CD	GLU	B	35	22.987	-4.587	7.744
ATOM	1242	OE1	GLU	B	35	21.980	-5.258	8.118
ATOM	1243	OE2	GLU	B	35	24.149	-4.860	8.048
ATOM	1244	N	MET	B	36	23.926	-2.106	10.157
ATOM	1245	H	MET	B	36	23.654	-2.953	10.613
ATOM	1246	CA	MET	B	36	25.232	-1.559	10.441
ATOM	1247	C	MET	B	36	26.146	-2.687	10.815
ATOM	1248	O	MET	B	36	25.731	-3.783	11.257
ATOM	1249	CB	MET	B	36	25.251	-0.424	11.497
ATOM	1250	CG	MET	B	36	24.626	-0.724	12.881
ATOM	1251	SD	MET	B	36	24.722	0.719	13.988
ATOM	1252	CE	MET	B	36	23.132	1.586	13.692
ATOM	1253	N	SER	B	37	27.441	-2.551	10.593
ATOM	1254	H	SER	B	37	27.783	-1.726	10.144
ATOM	1255	CA	SER	B	37	28.321	-3.608	11.011
ATOM	1256	C	SER	B	37	28.721	-3.352	12.442
ATOM	1257	O	SER	B	37	29.402	-2.369	12.788
ATOM	1258	CB	SER	B	37	29.567	-3.622	10.109
ATOM	1259	OG	SER	B	37	29.231	-3.908	8.750
ATOM	1260	HG	SER	B	37	30.057	-3.911	8.187
ATOM	1261	N	LEU	B	38	28.469	-4.295	13.366
ATOM	1262	H	LEU	B	38	27.948	-5.123	13.117
ATOM	1263	CA	LEU	B	38	29.073	-4.232	14.714
ATOM	1264	C	LEU	B	38	30.132	-5.342	14.895
ATOM	1265	O	LEU	B	38	30.070	-6.357	14.197
ATOM	1266	CB	LEU	B	38	27.986	-4.237	15.802
ATOM	1267	CG	LEU	B	38	27.005	-3.039	15.750
ATOM	1268	CD1	LEU	B	38	25.885	-3.214	16.788
ATOM	1269	CD2	LEU	B	38	27.707	-1.696	16.017
ATOM	1270	N	PRO	B	39	31.119	-5.160	15.804
ATOM	1271	CA	PRO	B	39	32.199	-6.116	16.052
ATOM	1272	C	PRO	B	39	31.767	-7.223	17.028
ATOM	1273	O	PRO	B	39	31.448	-6.942	18.185
ATOM	1274	CB	PRO	B	39	33.347	-5.276	16.625
ATOM	1275	CG	PRO	B	39	32.634	-4.148	17.370
ATOM	1276	CD	PRO	B	39	31.385	-3.916	16.523
ATOM	1277	N	GLY	B	40	31.770	-8.481	16.559
ATOM	1278	H	GLY	B	40	32.036	-8.641	15.598
ATOM	1279	CA	GLY	B	40	31.420	-9.658	17.353
ATOM	1280	C	GLY	B	40	30.679	-10.723	16.539
ATOM	1281	O	GLY	B	40	30.647	-10.671	15.308
ATOM	1282	N	LYS	B	41	30.098	-11.699	17.255
ATOM	1283	H	LYS	B	41	30.164	-11.656	18.261
ATOM	1284	CA	LYS	B	41	29.399	-12.861	16.702
ATOM	1285	C	LYS	B	41	27.971	-12.923	17.245
ATOM	1286	O	LYS	B	41	27.743	-12.700	18.436

Figure 11x

ATOM	1287	CB	LYS	B	41	30.154	-14.152	17.048
ATOM	1288	CG	LYS	B	41	31.537	-14.221	16.384
ATOM	1289	CD	LYS	B	41	32.192	-15.580	16.651
ATOM	1290	CE	LYS	B	41	33.566	-15.642	15.983
ATOM	1291	NZ	LYS	B	41	34.198	-16.956	16.183
ATOM	1292	1HZ	LYS	B	41	35.102	-16.968	15.732
ATOM	1293	3HZ	LYS	B	41	33.612	-17.674	15.782
ATOM	1294	2HZ	LYS	B	41	34.312	-17.128	17.172
ATOM	1295	N	TRP	B	42	27.018	-13.228	16.351
ATOM	1296	H	TRP	B	42	27.307	-13.458	15.411
ATOM	1297	CA	TRP	B	42	25.597	-12.929	16.521
ATOM	1298	C	TRP	B	42	24.723	-14.179	16.405
ATOM	1299	O	TRP	B	42	25.210	-15.277	16.131
ATOM	1300	CB	TRP	B	42	25.192	-11.856	15.491
ATOM	1301	CG	TRP	B	42	26.127	-10.687	15.390
ATOM	1302	CD1	TRP	B	42	26.651	-10.197	14.244
ATOM	1303	CD2	TRP	B	42	26.739	-9.913	16.467
ATOM	1304	NE1	TRP	B	42	27.548	-9.191	14.533
ATOM	1305	HE1	TRP	B	42	28.067	-8.702	13.818
ATOM	1306	CE2	TRP	B	42	27.664	-8.995	15.893
ATOM	1307	CE3	TRP	B	42	26.640	-9.923	17.875
ATOM	1308	CZ2	TRP	B	42	28.443	-8.136	16.680
ATOM	1309	CZ3	TRP	B	42	27.426	-9.075	18.673
ATOM	1310	CH2	TRP	B	42	28.318	-8.171	18.077
ATOM	1311	N	LYS	B	43	23.416	-13.980	16.617
ATOM	1312	H	LYS	B	43	23.105	-13.044	16.840
ATOM	1313	CA	LYS	B	43	22.378	-14.995	16.526
ATOM	1314	C	LYS	B	43	21.368	-14.507	15.478
ATOM	1315	O	LYS	B	43	20.743	-13.472	15.706
ATOM	1316	CB	LYS	B	43	21.694	-15.196	17.893
ATOM	1317	CG	LYS	B	43	22.641	-15.623	19.034
ATOM	1318	CD	LYS	B	43	22.409	-14.814	20.323
ATOM	1319	CE	LYS	B	43	22.767	-13.327	20.182
ATOM	1320	NZ	LYS	B	43	24.214	-13.113	20.015
ATOM	1321	1HZ	LYS	B	43	24.400	-12.125	19.924
ATOM	1322	3HZ	LYS	B	43	24.532	-13.593	19.185
ATOM	1323	2HZ	LYS	B	43	24.702	-13.476	20.821
ATOM	1324	N	PRO	B	44	21.175	-15.204	14.341
ATOM	1325	CA	PRO	B	44	20.139	-14.835	13.382
ATOM	1326	C	PRO	B	44	18.765	-14.997	14.044
ATOM	1327	O	PRO	B	44	18.573	-15.902	14.860
ATOM	1328	CB	PRO	B	44	20.341	-15.761	12.180
ATOM	1329	CG	PRO	B	44	20.999	-16.999	12.787
ATOM	1330	CD	PRO	B	44	21.837	-16.434	13.933
ATOM	1331	N	LYS	B	45	17.825	-14.101	13.712
ATOM	1332	H	LYS	B	45	17.994	-13.483	12.944
ATOM	1333	CA	LYS	B	45	16.523	-14.088	14.339
ATOM	1334	C	LYS	B	45	15.519	-13.590	13.329
ATOM	1335	O	LYS	B	45	15.829	-12.838	12.379
ATOM	1336	CB	LYS	B	45	16.558	-13.149	15.560
ATOM	1337	CG	LYS	B	45	15.469	-13.442	16.579
ATOM	1338	CD	LYS	B	45	15.256	-12.254	17.501
ATOM	1339	CE	LYS	B	45	14.131	-12.461	18.469
ATOM	1340	NZ	LYS	B	45	14.549	-13.442	19.474
ATOM	1341	1HZ	LYS	B	45	13.805	-13.588	20.126
ATOM	1342	3HZ	LYS	B	45	15.355	-13.101	19.958

Figure 11 y

ATOM	1343	2HZ	LYS	B	45	14.772	-14.306	19.023
ATOM	1344	N	MET	B	46	14.240	-14.005	13.416
ATOM	1345	H	MET	B	46	13.991	-14.705	14.085
ATOM	1346	CA	MET	B	46	13.203	-13.472	12.570
ATOM	1347	C	MET	B	46	12.291	-12.623	13.425
ATOM	1348	O	MET	B	46	11.782	-13.063	14.471
ATOM	1349	CB	MET	B	46	12.383	-14.616	12.016
ATOM	1350	CG	MET	B	46	13.153	-15.586	11.187
ATOM	1351	SD	MET	B	46	12.977	-15.188	9.473
ATOM	1352	CE	MET	B	46	13.566	-16.690	8.775
ATOM	1353	N	ILE	B	47	11.933	-11.379	13.030
ATOM	1354	H	ILE	B	47	12.327	-10.991	12.196
ATOM	1355	CA	ILE	B	47	10.971	-10.568	13.797
ATOM	1356	C	ILE	B	47	9.761	-10.233	12.962
ATOM	1357	O	ILE	B	47	9.819	-10.048	11.731
ATOM	1358	CB	ILE	B	47	11.608	-9.294	14.385
ATOM	1359	CG1	ILE	B	47	12.345	-8.459	13.318
ATOM	1360	CG2	ILE	B	47	12.542	-9.638	15.494
ATOM	1361	CD1	ILE	B	47	12.789	-7.123	13.851
ATOM	1362	N	GLY	B	48	8.557	-10.136	13.558
ATOM	1363	H	GLY	B	48	8.484	-10.249	14.549
ATOM	1364	CA	GLY	B	48	7.365	-9.872	12.800
ATOM	1365	C	GLY	B	48	6.826	-8.512	13.141
ATOM	1366	O	GLY	B	48	7.136	-7.832	14.149
ATOM	1367	N	GLY	B	49	5.940	-8.027	12.306
ATOM	1368	H	GLY	B	49	5.668	-8.562	11.506
ATOM	1369	CA	GLY	B	49	5.336	-6.745	12.493
ATOM	1370	C	GLY	B	49	4.082	-6.786	11.674
ATOM	1371	O	GLY	B	49	3.561	-7.847	11.273
ATOM	1372	N	ILE	B	50	3.531	-5.634	11.315
ATOM	1373	H	ILE	B	50	4.015	-4.777	11.492
ATOM	1374	CA	ILE	B	50	2.247	-5.573	10.673
ATOM	1375	C	ILE	B	50	2.118	-6.456	9.420
ATOM	1376	O	ILE	B	50	1.175	-7.253	9.215
ATOM	1377	CB	ILE	B	50	1.982	-4.071	10.391
ATOM	1378	CG1	ILE	B	50	1.005	-3.539	11.396
ATOM	1379	CG2	ILE	B	50	1.610	-3.739	8.922
ATOM	1380	CD1	ILE	B	50	-0.391	-4.077	11.252
ATOM	1381	N	GLY	B	51	3.113	-6.410	8.519
ATOM	1382	H	GLY	B	51	3.957	-5.920	8.737
ATOM	1383	CA	GLY	B	51	2.926	-7.075	7.259
ATOM	1384	C	GLY	B	51	3.671	-8.391	7.077
ATOM	1385	O	GLY	B	51	3.716	-8.945	5.973
ATOM	1386	N	GLY	B	52	4.296	-8.982	8.116
ATOM	1387	H	GLY	B	52	4.227	-8.580	9.029
ATOM	1388	CA	GLY	B	52	5.053	-10.190	7.874
ATOM	1389	C	GLY	B	52	6.334	-10.178	8.678
ATOM	1390	O	GLY	B	52	6.519	-9.421	9.657
ATOM	1391	N	PHE	B	53	7.325	-11.015	8.343
ATOM	1392	H	PHE	B	53	7.227	-11.603	7.540
ATOM	1393	CA	PHE	B	53	8.542	-11.096	9.110
ATOM	1394	C	PHE	B	53	9.727	-10.584	8.315
ATOM	1395	O	PHE	B	53	9.780	-10.618	7.075
ATOM	1396	CB	PHE	B	53	8.804	-12.555	9.542
ATOM	1397	CG	PHE	B	53	7.850	-13.023	10.592
ATOM	1398	CD1	PHE	B	53	6.513	-13.277	10.279

Figure 11 y

Figure 11Z

ATOM	1399	CD2	PHE	B	53	8.279	-13.192	11.918
ATOM	1400	CE1	PHE	B	53	5.620	-13.697	11.253
ATOM	1401	CE2	PHE	B	53	7.382	-13.615	12.903
ATOM	1402	CZ	PHE	B	53	6.052	-13.868	12.574
ATOM	1403	N	ILE	B	54	10.758	-10.126	8.985
ATOM	1404	H	ILE	B	54	10.665	-9.922	9.960
ATOM	1405	CA	ILE	B	54	12.029	-9.910	8.338
ATOM	1406	C	ILE	B	54	13.089	-10.648	9.134
ATOM	1407	O	ILE	B	54	12.952	-11.006	10.325
ATOM	1408	CB	ILE	B	54	12.390	-8.444	8.236
ATOM	1409	CG1	ILE	B	54	12.386	-7.775	9.611
ATOM	1410	CG2	ILE	B	54	11.460	-7.770	7.218
ATOM	1411	CD1	ILE	B	54	13.113	-6.438	9.590
ATOM	1412	N	LYS	B	55	14.272	-10.852	8.523
ATOM	1413	H	LYS	B	55	14.383	-10.599	7.562
ATOM	1414	CA	LYS	B	55	15.403	-11.431	9.216
ATOM	1415	C	LYS	B	55	16.274	-10.324	9.732
ATOM	1416	O	LYS	B	55	16.620	-9.328	9.047
ATOM	1417	CB	LYS	B	55	16.222	-12.237	8.245
ATOM	1418	CG	LYS	B	55	15.638	-13.596	8.063
ATOM	1419	CD	LYS	B	55	16.299	-14.348	6.953
ATOM	1420	CE	LYS	B	55	15.311	-14.520	5.813
ATOM	1421	NZ	LYS	B	55	15.757	-15.577	4.897
ATOM	1422	1HZ	LYS	B	55	15.095	-15.676	4.154
ATOM	1423	3HZ	LYS	B	55	15.830	-16.441	5.395
ATOM	1424	2HZ	LYS	B	55	16.650	-15.334	4.518
ATOM	1425	N	VAL	B	56	16.880	-10.547	10.910
ATOM	1426	H	VAL	B	56	16.741	-11.418	11.382
ATOM	1427	CA	VAL	B	56	17.732	-9.578	11.534
ATOM	1428	C	VAL	B	56	18.884	-10.304	12.184
ATOM	1429	O	VAL	B	56	18.884	-11.539	12.367
ATOM	1430	CB	VAL	B	56	16.912	-8.819	12.609
ATOM	1431	CG1	VAL	B	56	15.865	-7.943	11.921
ATOM	1432	CG2	VAL	B	56	16.215	-9.788	13.599
ATOM	1433	N	ARG	B	57	19.958	-9.593	12.591
ATOM	1434	H	ARG	B	57	20.030	-8.624	12.353
ATOM	1435	CA	ARG	B	57	21.050	-10.193	13.386
ATOM	1436	C	ARG	B	57	20.963	-9.608	14.804
ATOM	1437	O	ARG	B	57	20.814	-8.395	15.053
ATOM	1438	CB	ARG	B	57	22.426	-9.873	12.817
ATOM	1439	CG	ARG	B	57	22.664	-10.437	11.439
ATOM	1440	CD	ARG	B	57	24.012	-10.065	10.899
ATOM	1441	NE	ARG	B	57	24.280	-10.697	9.617
ATOM	1442	HE	ARG	B	57	23.592	-11.323	9.250
ATOM	1443	CZ	ARG	B	57	25.392	-10.478	8.921
ATOM	1444	NH1	ARG	B	57	26.337	-9.650	9.353
ATOM	1445	2HH1	ARG	B	57	26.223	-9.171	10.224
ATOM	1446	1HH1	ARG	B	57	27.163	-9.505	8.808
ATOM	1447	NH2	ARG	B	57	25.561	-11.104	7.760
ATOM	1448	1HH2	ARG	B	57	26.392	-10.950	7.225
ATOM	1449	2HH2	ARG	B	57	24.857	-11.729	7.422
ATOM	1450	N	GLN	B	58	20.997	-10.489	15.832
ATOM	1451	H	GLN	B	58	21.176	-11.456	15.650
ATOM	1452	CA	GLN	B	58	20.780	-10.072	17.206
ATOM	1453	C	GLN	B	58	22.108	-9.886	17.882
ATOM	1454	O	GLN	B	58	22.918	-10.815	18.038

Figure 11aa

ATOM	1455	CB	GLN	B	58	20.051	-11.190	17.932
ATOM	1456	CG	GLN	B	58	19.765	-10.845	19.366
ATOM	1457	CD	GLN	B	58	19.179	-12.003	20.112
ATOM	1458	OE1	GLN	B	58	19.712	-12.472	21.101
ATOM	1459	NE2	GLN	B	58	18.055	-12.476	19.623
ATOM	1460	1HE2	GLN	B	58	17.598	-13.249	20.063
ATOM	1461	2HE2	GLN	B	58	17.647	-12.066	18.807
ATOM	1462	N	TYR	B	59	22.416	-8.692	18.422
ATOM	1463	H	TYR	B	59	21.788	-7.921	18.311
ATOM	1464	CA	TYR	B	59	23.631	-8.486	19.161
ATOM	1465	C	TYR	B	59	23.244	-8.290	20.607
ATOM	1466	O	TYR	B	59	22.178	-7.728	20.927
ATOM	1467	CB	TYR	B	59	24.387	-7.241	18.653
ATOM	1468	CG	TYR	B	59	24.271	-7.075	17.149
ATOM	1469	CD1	TYR	B	59	23.045	-7.242	16.494
ATOM	1470	CD2	TYR	B	59	25.385	-6.753	16.374
ATOM	1471	CE1	TYR	B	59	22.939	-7.093	15.112
ATOM	1472	CE2	TYR	B	59	25.291	-6.603	14.995
ATOM	1473	CZ	TYR	B	59	24.068	-6.774	14.365
ATOM	1474	OH	TYR	B	59	24.018	-6.620	13.010
ATOM	1475	HH	TYR	B	59	24.926	-6.394	12.658
ATOM	1476	N	ASP	B	60	24.010	-8.785	21.596
ATOM	1477	H	ASP	B	60	24.852	-9.276	21.372
ATOM	1478	CA	ASP	B	60	23.644	-8.624	22.992
ATOM	1479	C	ASP	B	60	24.556	-7.595	23.615
ATOM	1480	O	ASP	B	60	25.654	-7.261	23.125
ATOM	1481	CB	ASP	B	60	23.789	-9.920	23.777
ATOM	1482	CG	ASP	B	60	22.803	-10.960	23.332
ATOM	1483	OD1	ASP	B	60	21.619	-10.634	23.032
ATOM	1484	OD2	ASP	B	60	23.208	-12.126	23.273
ATOM	1485	N	GLN	B	61	24.156	-7.022	24.774
ATOM	1486	H	GLN	B	61	23.252	-7.234	25.146
ATOM	1487	CA	GLN	B	61	25.011	-6.086	25.519
ATOM	1488	C	GLN	B	61	25.411	-4.866	24.746
ATOM	1489	O	GLN	B	61	26.560	-4.382	24.832
ATOM	1490	CB	GLN	B	61	26.269	-6.763	26.028
ATOM	1491	CG	GLN	B	61	26.020	-8.038	26.753
ATOM	1492	CD	GLN	B	61	25.714	-7.766	28.185
ATOM	1493	OE1	GLN	B	61	24.572	-7.455	28.548
ATOM	1494	NE2	GLN	B	61	26.744	-7.844	29.014
ATOM	1495	1HE2	GLN	B	61	26.620	-7.675	29.992
ATOM	1496	2HE2	GLN	B	61	27.654	-8.073	28.669
ATOM	1497	N	ILE	B	62	24.539	-4.257	23.933
ATOM	1498	H	ILE	B	62	23.628	-4.648	23.801
ATOM	1499	CA	ILE	B	62	24.878	-3.047	23.238
ATOM	1500	C	ILE	B	62	24.571	-1.885	24.144
ATOM	1501	O	ILE	B	62	23.515	-1.819	24.819
ATOM	1502	CB	ILE	B	62	24.097	-2.922	21.912
ATOM	1503	CG1	ILE	B	62	24.310	-4.170	21.094
ATOM	1504	CG2	ILE	B	62	24.568	-1.709	21.067
ATOM	1505	CD1	ILE	B	62	25.794	-4.479	20.878
ATOM	1506	N	LEU	B	63	25.485	-0.912	24.304
ATOM	1507	H	LEU	B	63	26.403	-1.028	23.926
ATOM	1508	CA	LEU	B	63	25.192	0.322	25.015

Figure 11bb

ATOM	1511	CB	LEU	B	63	26.436	0.970	25.590
ATOM	1512	CG	LEU	B	63	26.186	2.358	26.226
ATOM	1513	CD1	LEU	B	63	25.486	2.261	27.576
ATOM	1514	CD2	LEU	B	63	27.468	3.162	26.382
ATOM	1515	N	ILE	B	64	23.492	1.946	24.358
ATOM	1516	H	ILE	B	64	22.958	1.643	25.148
ATOM	1517	CA	ILE	B	64	23.003	3.068	23.617
ATOM	1518	C	ILE	B	64	22.872	4.194	24.612
ATOM	1519	O	ILE	B	64	22.915	4.007	25.846
ATOM	1520	CB	ILE	B	64	21.634	2.701	22.989
ATOM	1521	CG1	ILE	B	64	21.825	1.521	22.029
ATOM	1522	CG2	ILE	B	64	20.982	3.894	22.246
ATOM	1523	CD1	ILE	B	64	20.593	1.096	21.260
ATOM	1524	N	GLU	B	65	22.803	5.460	24.172
ATOM	1525	H	GLU	B	65	23.013	5.664	23.216
ATOM	1526	CA	GLU	B	65	22.432	6.551	25.037
ATOM	1527	C	GLU	B	65	21.242	7.194	24.373
ATOM	1528	O	GLU	B	65	21.312	7.729	23.257
ATOM	1529	CB	GLU	B	65	23.497	7.615	25.131
ATOM	1530	CG	GLU	B	65	24.787	7.196	25.761
ATOM	1531	CD	GLU	B	65	25.694	8.385	26.076
ATOM	1532	OE1	GLU	B	65	25.170	9.510	26.311
ATOM	1533	OE2	GLU	B	65	26.938	8.200	26.092
ATOM	1534	N	ILE	B	66	20.078	7.240	25.035
ATOM	1535	H	ILE	B	66	20.010	6.835	25.947
ATOM	1536	CA	ILE	B	66	18.907	7.865	24.462
ATOM	1537	C	ILE	B	66	18.777	9.195	25.145
ATOM	1538	O	ILE	B	66	18.591	9.303	26.379
ATOM	1539	CB	ILE	B	66	17.713	6.995	24.790
ATOM	1540	CG1	ILE	B	66	17.916	5.583	24.335
ATOM	1541	CG2	ILE	B	66	16.405	7.544	24.177
ATOM	1542	CD1	ILE	B	66	16.888	4.677	24.884
ATOM	1543	N	CYS	B	67	18.965	10.325	24.437
ATOM	1544	H	CYS	B	67	19.201	10.268	23.467
ATOM	1545	CA	CYS	B	67	18.833	11.663	25.049
ATOM	1546	C	CYS	B	67	19.637	11.781	26.319
ATOM	1547	O	CYS	B	67	19.235	12.400	27.328
ATOM	1548	CB	CYS	B	67	17.387	12.023	25.319
ATOM	1549	SG	CYS	B	67	16.407	12.259	23.821
ATOM	1550	N	GLY	B	68	20.830	11.180	26.383
ATOM	1551	H	GLY	B	68	21.158	10.646	25.604
ATOM	1552	CA	GLY	B	68	21.654	11.288	27.558
ATOM	1553	C	GLY	B	68	21.464	10.185	28.584
ATOM	1554	O	GLY	B	68	22.174	10.128	29.606
ATOM	1555	N	HIS	B	69	20.513	9.255	28.425
ATOM	1556	H	HIS	B	69	19.924	9.282	27.618
ATOM	1557	CA	HIS	B	69	20.304	8.199	29.391
ATOM	1558	C	HIS	B	69	20.861	6.936	28.811
ATOM	1559	O	HIS	B	69	20.589	6.560	27.647
ATOM	1560	CB	HIS	B	69	18.832	7.992	29.654
ATOM	1561	CG	HIS	B	69	18.175	9.203	30.223
ATOM	1562	ND1	HIS	B	69	17.504	9.195	31.435
ATOM	1563	HD1	HIS	B	69	17.383	8.402	32.032
ATOM	1564	CD2	HIS	B	69	18.122	10.470	29.729
ATOM	1565	CE1	HIS	B	69	17.070	10.429	31.626
ATOM	1566	NE2	HIS	B	69	17.410	11.240	30.635



Figure 11 cc

ATOM	1567	N	LYS	B	70	21.751	6.217	29.499
ATOM	1568	H	LYS	B	70	22.025	6.512	30.414
ATOM	1569	CA	LYS	B	70	22.326	5.020	28.945
ATOM	1570	C	LYS	B	70	21.386	3.854	29.145
ATOM	1571	O	LYS	B	70	20.627	3.725	30.120
ATOM	1572	CB	LYS	B	70	23.613	4.678	29.663
ATOM	1573	CG	LYS	B	70	24.694	5.655	29.379
ATOM	1574	CD	LYS	B	70	25.739	5.524	30.444
ATOM	1575	CE	LYS	B	70	27.048	6.090	30.011
ATOM	1576	NZ	LYS	B	70	26.948	7.548	30.000
ATOM	1577	1HZ	LYS	B	70	27.821	7.940	29.711
ATOM	1578	3HZ	LYS	B	70	26.725	7.874	30.919
ATOM	1579	2HZ	LYS	B	70	26.230	7.828	29.363
ATOM	1580	N	ALA	B	71	21.512	2.849	28.284
ATOM	1581	H	ALA	B	71	22.141	2.934	27.512
ATOM	1582	CA	ALA	B	71	20.762	1.630	28.432
ATOM	1583	C	ALA	B	71	21.629	0.576	27.805
ATOM	1584	O	ALA	B	71	22.463	0.830	26.912
ATOM	1585	CB	ALA	B	71	19.452	1.726	27.737
ATOM	1586	N	ILE	B	72	21.547	-0.681	28.237
ATOM	1587	H	ILE	B	72	20.864	-0.925	28.926
ATOM	1588	CA	ILE	B	72	22.424	-1.698	27.730
ATOM	1589	C	ILE	B	72	21.615	-2.938	27.462
ATOM	1590	O	ILE	B	72	20.909	-3.490	28.330
ATOM	1591	CB	ILE	B	72	23.524	-1.999	28.737
ATOM	1592	CG1	ILE	B	72	24.322	-0.735	29.090
ATOM	1593	CG2	ILE	B	72	24.442	-3.037	28.153
ATOM	1594	CD1	ILE	B	72	25.374	-1.012	30.163
ATOM	1595	N	GLY	B	73	21.609	-3.446	26.235
ATOM	1596	H	GLY	B	73	22.204	-3.054	25.534
ATOM	1597	CA	GLY	B	73	20.707	-4.545	26.062
ATOM	1598	C	GLY	B	73	20.828	-5.084	24.663
ATOM	1599	O	GLY	B	73	21.754	-4.831	23.863
ATOM	1600	N	THR	B	74	19.856	-5.905	24.271
ATOM	1601	H	THR	B	74	19.086	-6.088	24.882
ATOM	1602	CA	THR	B	74	19.869	-6.548	22.988
ATOM	1603	C	THR	B	74	19.363	-5.590	21.931
ATOM	1604	O	THR	B	74	18.338	-4.870	22.053
ATOM	1605	CB	THR	B	74	19.011	-7.801	23.074
ATOM	1606	OG1	THR	B	74	19.611	-8.683	24.013
ATOM	1607	HG1	THR	B	74	19.068	-9.519	24.092
ATOM	1608	CG2	THR	B	74	18.817	-8.496	21.705
ATOM	1609	N	VAL	B	75	20.028	-5.620	20.762
ATOM	1610	H	VAL	B	75	20.835	-6.203	20.666
ATOM	1611	CA	VAL	B	75	19.630	-4.837	19.611
ATOM	1612	C	VAL	B	75	19.600	-5.771	18.426
ATOM	1613	O	VAL	B	75	20.444	-6.673	18.230
ATOM	1614	CB	VAL	B	75	20.667	-3.712	19.395
ATOM	1615	CG1	VAL	B	75	20.473	-3.002	18.046
ATOM	1616	CG2	VAL	B	75	20.679	-2.708	20.567
ATOM	1617	N	LEU	B	76	18.557	-5.647	17.565
ATOM	1618	H	LEU	B	76	17.822	-5.000	17.767
ATOM	1619	CA	LEU	B	76	18.444	-6.427	16.324
ATOM	1620	C	LEU	B	76	18.736	-5.487	15.144
ATOM	1621	O	LEU	B	76	18.239	-4.343	15.040
ATOM	1622	CB	LEU	B	76	17.028	-7.021	16.158

Figure 11dd

ATOM	1623	CG	LEU	B	76	16.427	-7.612	17.449
ATOM	1624	CD1	LEU	B	76	14.992	-8.075	17.263
ATOM	1625	CD2	LEU	B	76	17.266	-8.758	18.019
ATOM	1626	N	VAL	B	77	19.607	-5.900	14.222
ATOM	1627	H	VAL	B	77	19.985	-6.824	14.276
ATOM	1628	CA	VAL	B	77	20.027	-5.042	13.133
ATOM	1629	C	VAL	B	77	19.570	-5.662	11.842
ATOM	1630	O	VAL	B	77	19.678	-6.883	11.598
ATOM	1631	CB	VAL	B	77	21.563	-4.905	13.191
ATOM	1632	CG1	VAL	B	77	22.129	-4.202	11.944
ATOM	1633	CG2	VAL	B	77	22.030	-4.166	14.470
ATOM	1634	N	GLY	B	78	18.978	-4.915	10.943
ATOM	1635	H	GLY	B	78	18.841	-3.941	11.121
ATOM	1636	CA	GLY	B	78	18.523	-5.475	9.705
ATOM	1637	C	GLY	B	78	18.019	-4.338	8.874
ATOM	1638	O	GLY	B	78	18.130	-3.142	9.223
ATOM	1639	N	PRO	B	79	17.408	-4.596	7.722
ATOM	1640	CA	PRO	B	79	16.954	-3.535	6.834
ATOM	1641	C	PRO	B	79	15.635	-2.872	7.280
ATOM	1642	O	PRO	B	79	14.609	-2.877	6.565
ATOM	1643	CB	PRO	B	79	16.804	-4.274	5.492
ATOM	1644	CG	PRO	B	79	16.463	-5.712	5.881
ATOM	1645	CD	PRO	B	79	17.159	-5.959	7.189
ATOM	1646	N	THR	B	80	15.574	-2.247	8.458
ATOM	1647	H	THR	B	80	16.374	-2.242	9.058
ATOM	1648	CA	THR	B	80	14.364	-1.583	8.865
ATOM	1649	C	THR	B	80	14.312	-0.189	8.228
ATOM	1650	O	THR	B	80	15.349	0.471	8.001
ATOM	1651	CB	THR	B	80	14.250	-1.512	10.410
ATOM	1652	OG1	THR	B	80	13.079	-0.802	10.806
ATOM	1653	HG1	THR	B	80	13.022	-0.766	11.804
ATOM	1654	CG2	THR	B	80	15.519	-0.901	11.062
ATOM	1655	N	PRO	B	81	13.137	0.354	7.885
ATOM	1656	CA	PRO	B	81	13.036	1.747	7.379
ATOM	1657	C	PRO	B	81	13.363	2.732	8.484
ATOM	1658	O	PRO	B	81	13.791	3.880	8.250
ATOM	1659	CB	PRO	B	81	11.548	1.912	6.982
ATOM	1660	CG	PRO	B	81	10.819	0.674	7.488
ATOM	1661	CD	PRO	B	81	11.854	-0.387	7.797
ATOM	1662	N	VAL	B	82	13.197	2.368	9.772
ATOM	1663	H	VAL	B	82	12.940	1.427	9.992
ATOM	1664	CA	VAL	B	82	13.380	3.306	10.885
ATOM	1665	C	VAL	B	82	14.160	2.668	12.010
ATOM	1666	O	VAL	B	82	14.045	1.465	12.293
ATOM	1667	CB	VAL	B	82	11.996	3.695	11.431
ATOM	1668	CG1	VAL	B	82	12.055	4.961	12.269
ATOM	1669	CG2	VAL	B	82	10.958	3.857	10.318
ATOM	1670	N	ASN	B	83	14.963	3.422	12.775
ATOM	1671	H	ASN	B	83	15.147	4.370	12.516
ATOM	1672	CA	ASN	B	83	15.550	2.846	13.967
ATOM	1673	C	ASN	B	83	14.481	2.874	15.022
ATOM	1674	O	ASN	B	83	13.814	3.903	15.294
ATOM	1675	CB	ASN	B	83	16.743	3.639	14.472
ATOM	1676	CG	ASN	B	83	17.935	3.574	13.570
ATOM	1677	OD1	ASN	B	83	18.409	2.511	13.167
ATOM	1678	ND2	ASN	B	83	18.439	4.735	13.238

Figure 11<sub>ee</sub>

ATOM	1679	2HD2	ASN	B	83	19.237	4.786	12.638
ATOM	1680	1HD2	ASN	B	83	18.030	5.580	13.582
ATOM	1681	N	ILE	B	84	14.225	1.749	15.711
ATOM	1682	H	ILE	B	84	14.791	0.938	15.564
ATOM	1683	CA	ILE	B	84	13.154	1.658	16.667
ATOM	1684	C	ILE	B	84	13.740	1.317	18.020
ATOM	1685	O	ILE	B	84	14.428	0.300	18.223
ATOM	1686	CB	ILE	B	84	12.214	0.517	16.260
ATOM	1687	CG1	ILE	B	84	11.656	0.759	14.849
ATOM	1688	CG2	ILE	B	84	11.128	0.247	17.315
ATOM	1689	CD1	ILE	B	84	10.770	-0.359	14.291
ATOM	1690	N	ILE	B	85	13.483	2.157	19.051
ATOM	1691	H	ILE	B	85	13.028	3.030	18.877
ATOM	1692	CA	ILE	B	85	13.846	1.834	20.408
ATOM	1693	C	ILE	B	85	12.596	1.254	21.085
ATOM	1694	O	ILE	B	85	11.536	1.903	21.267
ATOM	1695	CB	ILE	B	85	14.308	3.115	21.137
ATOM	1696	CG1	ILE	B	85	15.447	3.826	20.395
ATOM	1697	CG2	ILE	B	85	14.673	2.840	22.589
ATOM	1698	CD1	ILE	B	85	16.730	3.053	20.263
ATOM	1699	N	GLY	B	86	12.617	-0.052	21.422
ATOM	1700	H	GLY	B	86	13.439	-0.595	21.251
ATOM	1701	CA	GLY	B	86	11.481	-0.702	22.028
ATOM	1702	C	GLY	B	86	11.557	-0.748	23.538
ATOM	1703	O	GLY	B	86	12.412	-0.165	24.238
ATOM	1704	N	ARG	B	87	10.614	-1.489	24.149
ATOM	1705	H	ARG	B	87	10.012	-2.072	23.604
ATOM	1706	CA	ARG	B	87	10.442	-1.468	25.584
ATOM	1707	C	ARG	B	87	11.627	-2.021	26.326
ATOM	1708	O	ARG	B	87	11.911	-1.666	27.495
ATOM	1709	CB	ARG	B	87	9.200	-2.271	25.949
ATOM	1710	CG	ARG	B	87	7.951	-1.960	25.161
ATOM	1711	CD	ARG	B	87	6.956	-3.074	25.219
ATOM	1712	NE	ARG	B	87	5.906	-2.933	24.205
ATOM	1713	HE	ARG	B	87	5.790	-2.039	23.772
ATOM	1714	CZ	ARG	B	87	5.119	-3.953	23.856
ATOM	1715	NH1	ARG	B	87	5.252	-5.161	24.396
ATOM	1716	2HH1	ARG	B	87	5.958	-5.326	25.085
ATOM	1717	1HH1	ARG	B	87	4.646	-5.905	24.113
ATOM	1718	NH2	ARG	B	87	4.180	-3.751	22.939
ATOM	1719	1HH2	ARG	B	87	3.580	-4.502	22.664
ATOM	1720	2HH2	ARG	B	87	4.073	-2.848	22.524
ATOM	1721	N	ASN	B	88	12.413	-2.937	25.731
ATOM	1722	H	ASN	B	88	12.206	-3.237	24.800
ATOM	1723	CA	ASN	B	88	13.582	-3.519	26.415
ATOM	1724	C	ASN	B	88	14.532	-2.429	26.821
ATOM	1725	O	ASN	B	88	15.214	-2.516	27.863
ATOM	1726	CB	ASN	B	88	14.285	-4.605	25.559
ATOM	1727	CG	ASN	B	88	15.063	-4.031	24.358
ATOM	1728	OD1	ASN	B	88	14.515	-3.245	23.612
ATOM	1729	ND2	ASN	B	88	16.333	-4.445	24.180
ATOM	1730	2HD2	ASN	B	88	16.875	-4.099	23.414
ATOM	1731	1HD2	ASN	B	88	16.744	-5.102	24.812
ATOM	1732	N	LEU	B	89	14.695	-1.328	26.061
ATOM	1733	H	LEU	B	89	14.192	-1.240	25.201
ATOM	1734	CA	LEU	B	89	15.597	-0.234	26.452

Figure 11ff

ATOM	1735	C	LEU	B	89	14.797	0.937	27.053
ATOM	1736	O	LEU	B	89	15.293	1.734	27.879
ATOM	1737	CB	LEU	B	89	16.421	0.232	25.236
ATOM	1738	CG	LEU	B	89	17.400	-0.754	24.567
ATOM	1739	CD1	LEU	B	89	18.215	0.002	23.573
ATOM	1740	CD2	LEU	B	89	18.352	-1.458	25.570
ATOM	1741	N	LEU	B	90	13.511	1.114	26.705
ATOM	1742	H	LEU	B	90	13.082	0.486	26.056
ATOM	1743	CA	LEU	B	90	12.698	2.221	27.257
ATOM	1744	C	LEU	B	90	12.537	2.060	28.751
ATOM	1745	O	LEU	B	90	12.575	3.033	29.533
ATOM	1746	CB	LEU	B	90	11.311	2.258	26.628
ATOM	1747	CG	LEU	B	90	11.232	2.730	25.168
ATOM	1748	CD1	LEU	B	90	9.808	2.744	24.642
ATOM	1749	CD2	LEU	B	90	11.831	4.105	24.982
ATOM	1750	N	THR	B	91	12.315	0.843	29.271
ATOM	1751	H	THR	B	91	12.218	0.055	28.663
ATOM	1752	CA	THR	B	91	12.210	0.634	30.699
ATOM	1753	C	THR	B	91	13.537	1.028	31.375
ATOM	1754	O	THR	B	91	13.575	1.525	32.518
ATOM	1755	CB	THR	B	91	11.893	-0.843	31.028
ATOM	1756	OG1	THR	B	91	12.919	-1.676	30.504
ATOM	1757	HG1	THR	B	91	12.722	-2.634	30.713
ATOM	1758	CG2	THR	B	91	10.599	-1.285	30.418
ATOM	1759	N	GLN	B	92	14.705	0.852	30.732
ATOM	1760	H	GLN	B	92	14.707	0.497	29.797
ATOM	1761	CA	GLN	B	92	15.920	1.190	31.433
ATOM	1762	C	GLN	B	92	16.088	2.660	31.633
ATOM	1763	O	GLN	B	92	16.807	3.137	32.527
ATOM	1764	CB	GLN	B	92	17.127	0.680	30.682
ATOM	1765	CG	GLN	B	92	17.076	-0.805	30.517
ATOM	1766	CD	GLN	B	92	18.336	-1.314	29.900
ATOM	1767	OE1	GLN	B	92	19.394	-0.720	30.059
ATOM	1768	NE2	GLN	B	92	18.221	-2.411	29.195
ATOM	1769	1HE2	GLN	B	92	19.022	-2.813	28.751
ATOM	1770	2HE2	GLN	B	92	17.331	-2.856	29.095
ATOM	1771	N	ILE	B	93	15.538	3.512	30.746
ATOM	1772	H	ILE	B	93	15.016	3.153	29.972
ATOM	1773	CA	ILE	B	93	15.693	4.937	30.899
ATOM	1774	C	ILE	B	93	14.522	5.549	31.698
ATOM	1775	O	ILE	B	93	14.438	6.773	31.940
ATOM	1776	CB	ILE	B	93	15.981	5.657	29.548
ATOM	1777	CG1	ILE	B	93	14.746	5.718	28.619
ATOM	1778	CG2	ILE	B	93	17.223	5.060	28.874
ATOM	1779	CD1	ILE	B	93	14.946	6.734	27.488
ATOM	1780	N	GLY	B	94	13.617	4.731	32.263
ATOM	1781	H	GLY	B	94	13.639	3.752	32.060
ATOM	1782	CA	GLY	B	94	12.594	5.224	33.170
ATOM	1783	C	GLY	B	94	11.443	5.846	32.432
ATOM	1784	O	GLY	B	94	10.766	6.803	32.878
ATOM	1785	N	CYS	B	95	11.134	5.354	31.225
ATOM	1786	H	CYS	B	95	11.603	4.538	30.888
ATOM	1787	CA	CYS	B	95	10.134	5.969	30.381
ATOM	1788	C	CYS	B	95	8.750	5.512	30.764
ATOM	1789	O	CYS	B	95	8.478	4.309	31.006
ATOM	1790	CB	CYS	B	95	10.456	5.643	28.922

00000000000000000000

Figure 1199

ATOM	1791	SG	CYS	B	95	9.426	6.512	27.764
ATOM	1792	N	THR	B	96	7.778	6.444	30.764
ATOM	1793	H	THR	B	96	8.014	7.401	30.539
ATOM	1794	CA	THR	B	96	6.379	6.163	31.108
ATOM	1795	C	THR	B	96	5.390	6.970	30.254
ATOM	1796	O	THR	B	96	5.567	8.171	30.066
ATOM	1797	CB	THR	B	96	6.111	6.439	32.604
ATOM	1798	OG1	THR	B	96	6.341	7.794	32.938
ATOM	1799	HG1	THR	B	96	6.111	7.924	33.861
ATOM	1800	CG2	THR	B	96	6.938	5.566	33.554
ATOM	1801	N	LEU	B	97	4.302	6.321	29.809
ATOM	1802	H	LEU	B	97	4.216	5.332	29.997
ATOM	1803	CA	LEU	B	97	3.127	6.986	29.238
ATOM	1804	C	LEU	B	97	2.336	7.681	30.358
ATOM	1805	O	LEU	B	97	2.350	7.221	31.499
ATOM	1806	CB	LEU	B	97	2.226	5.958	28.532
ATOM	1807	CG	LEU	B	97	2.860	5.279	27.300
ATOM	1808	CD1	LEU	B	97	2.101	3.986	26.957
ATOM	1809	CD2	LEU	B	97	2.842	6.216	26.085
ATOM	1810	N	ASN	B	98	1.637	8.777	30.024
ATOM	1811	H	ASN	B	98	1.662	9.086	29.063
ATOM	1812	CA	ASN	B	98	0.906	9.631	30.960
ATOM	1813	C	ASN	B	98	-0.251	10.321	30.231
ATOM	1814	O	ASN	B	98	-0.032	11.303	29.522
ATOM	1815	CB	ASN	B	98	1.845	10.678	31.587
ATOM	1816	CG	ASN	B	98	2.783	10.077	32.634
ATOM	1817	OD1	ASN	B	98	3.926	9.739	32.335
ATOM	1818	ND2	ASN	B	98	2.297	9.942	33.870
ATOM	1819	2HD2	ASN	B	98	2.877	9.551	34.599
ATOM	1820	1HD2	ASN	B	98	1.351	10.229	34.074
ATOM	1821	N	LEU	B	99	-1.476	9.808	30.426
ATOM	1822	H	LEU	B	99	-1.568	9.010	31.037
ATOM	1823	CA	LEU	B	99	-2.709	10.288	29.797
ATOM	1824	C	LEU	B	99	-3.816	10.589	30.815
ATOM	1825	O	LEU	B	99	-3.630	10.272	32.011
ATOM	1826	CB	LEU	B	99	-3.146	9.340	28.657
ATOM	1827	CG	LEU	B	99	-3.714	7.932	28.941
ATOM	1828	CD1	LEU	B	99	-2.767	7.057	29.774
ATOM	1829	CD2	LEU	B	99	-5.134	7.943	29.528
ATOM	1830	OXT	LEU	B	99	-4.842	11.156	30.376
TER								

# SEQUENCE LISTING

<110> Kalyanaraman Ramnarayan  
Edward T. Maggio  
P. Patrick Hess

<120> Use of Computationally Derived Protein  
Structures of Genetic Polymorphisms in Pharmacogenomics for  
Drug Design and Clinical Applications

<130> 24737-1906C

<140> Unassigned

<141> 2000-11-10

<150> 09/438,566

<151> 1999-11-10

<150> 24737-1906B

<151> 2000-11-01

<160> 118

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Modified Hepatitis C Virus NS3 Protease Inhibitor  
Peptide

<221> ACETYLATION

<222> 1

<221> MOD\_RES

<222> 2

<223> D-glutamic acid

<221> MOD\_RES

<222> 5

<223> beta-cyclohexylalanine

<300>

<301> Ingallinella, P., Altamura, S., Bianchi, E., Talia

<302> Potent Peptide Inhibitors Of Human Hepatitis C Vir

<303> Biochemistry

<304> 37

<305> 25

<306> 8906-8914

<307> 1998-06-23

<400> 1

Asp Xaa Leu Ile Xaa Cys

1

5

<210> 2

<211> 6

<212> PRT

<213> Artificial Sequence



100	105	110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu			384
115	120	125	
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa gga Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly			432
130	135	140	
aaa att tca aaa att ggg cct gag aat cca tac aat act cca ata ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe			480
145	150	155	160
gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe			528
	165	170	175
aga gaa ctt aat aag aga aca caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly			576
	180	185	190
ata cca cac ccc gca ggg tta aaa cag aaa aaa tca gta aca ata ctg Ile Pro His Pro Ala Gly Leu Lys Gln Lys Lys Ser Val Thr Ile Leu			624
	195	200	205
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat gaa ggc ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Gly Phe Arg			672
210	215	220	
aag tat act gca ttt acc ata cct agt aga aat aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Arg Asn Asn Glu Thr Pro Gly			720
225	230	235	240
att aga tat cag tac aac gtg ctc cca cag gga tgg aaa gga tca cca Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro			768
	245	250	255
gca ata ttt caa agt agc atg aca aga aty tta gag cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Arg Xaa Leu Glu Pro Phe Arg Lys			816
	260	265	270
caa aat cca gaa ata gtt atc tat caa tac atg gat gat ttg tat gta Gln Asn Pro Glu Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val			864
	275	280	285
gga tct gac tta gaa ata gga cag cat aga gca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Ala Lys Ile Glu Glu Leu			912
290	295	300	
aga gga cat cta tta aag tgg gga ttt acc aca cca gac aaa aaa cat Arg Gly His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His			960
305	310	315	320
cag aaa gaa cct cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			1008
	325	330	335
aaa tgg aca gta cag cct ata aag ttg cca gaa aaa g Lys Trp Thr Val Gln Pro Ile Lys Leu Pro Glu Lys			1045
	340	345	

<210> 4  
 <211> 1046  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)



<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1046)  
 <223> Portion of HIV Reverse Transcriptase

<400> 4  
 cct cag atc act ctt tgg caa cga ccc ctt gtc aca ata aag ata gga 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly  
 1 5 10 15  
 ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gta 96  
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
 20 25 30  
 gtt gaa gaa atg aat ttg cca gga aaa tgg aaa cca aaa atg ata ggg 144  
 Val Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly  
 35 40 45  
 gga att gga ggt ttt atc aaa gta aga cag tat gag caa ata gcc gta 192  
 Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Glu Gln Ile Ala Val  
 50 55 60  
 gaa aty tgt gga cat aga gct atg ggt aca gta tta gta gga cct aca 240  
 Glu Xaa Cys Gly His Arg Ala Met Gly Thr Val Leu Val Gly Pro Thr  
 65 70 75 80  
 cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act 288  
 Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr  
 85 90 95  
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
 100 105 110  
 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
 115 120 125  
 aaa ata aaa gca tta gta gaa atc tgt aca gaa ttg gaa aag gaa ggg 432  
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly  
 130 135 140  
 aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt 480  
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
 145 150 155 160  
 gcc ata aag aaa aag aac agt act aaa tgg aga aaa tta gta gat ttc 528  
 Ala Ile Lys Lys Lys Asn Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
 165 170 175  
 aga gaa ctt aat aag aga act caa gac ttc tgg gag gtt caa tta gga 576  
 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
 180 185 190  
 ata cca cat cca gca ggg tta aaa aag aat aaa tca ata aca gta ctg 624  
 Ile Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Ile Thr Val Leu  
 195 200 205  
 gat gtg ggt gat gca tat ttt tca gtt ccc tta tgt gaa gac ttc agg 672  
 Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Cys Glu Asp Phe Arg  
 210 215 220  
 aag tat act gca ttt acc ata cct agt gta aac aat gag act cca ggg 720

Lys 225	Tyr	Thr	Ala	Phe	Thr 230	Ile	Pro	Ser	Val	Asn 235	Asn	Glu	Thr	Pro	Gly 240	
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	ttc Phe 255	acc Thr	768
agc Ser	ata Ile	ttc Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gag Glu	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	gca Ala	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	tat Tyr	ctg Leu	tgg Trp	aag Lys 310	tgg Trp	gga Gly	ttt Phe	tgc Cys	aca Thr 315	cca Pro	gaa Glu	caa Gln	aar Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cct Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggg Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	ccc Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	caa Gln	cct Pro	ata Ile	gtg Val 345	ctg Leu	cca Pro	gac Asp	aaa Lys	ga				1046
<210> 5																
<211> 1104																
<212> DNA																
<213> Human Immunodeficiency Virus (HIV)																
<220>																
<221> CDS																
<222> (0) ... (297)																
<223> HIV Protease																
<221> CDS																
<222> (298) ... (1104)																
<223> Portion of HIV Reverse Transcriptase																
<400> 5																
cct Pro 1	cag Gln	atc Ile	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	atc Ile 10	gtc Val	aca Thr	ata Ile	aag Lys 15	rta Xaa	ggg Gly	48
ggg Gly	caa Gln	cta Leu	agg Arg 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp 30	gat Asp 30	aca Thr	ata Ile	96
ata Ile	gaa Glu	gac Asp 35	ata Ile	act Thr	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aca Thr	cca Pro	aaa Lys 45	atg Met	ata Ile	ggg Gly	144
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	gtc Val	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag				

cca ata aac ata gtt gga aga aat ctg atg act cag att ggt tgc act	288
Pro Ile Asn Ile Val Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr	
85 90 95	
tta aat ttt ccc att agt cct att gaa act gta cca gtc aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aag gca tta gta gaa att tgt mca gaa ctg gaa atg gat gga	432
Lys Ile Lys Ala Leu Val Glu Ile Cys Xaa Glu Leu Glu Met Asp Gly	
130 135 140	
aaa att tca aaa att ggg cct gaa aat ccg tac aat act cca gta ttt	480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe	
145 150 155 160	
gcc ata aag aaa aag aac agt act aaa tgg aga aaa tta gta gat ttc	528
Ala Ile Lys Lys Lys Asn Ser Thr Lys Trp Arg Lys Leu Val Asp Phe	
165 170 175	
aga gaa ctt aac aaa aga act caa gac ttc tgg aga aaa tta gga	576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly	
180 185 190	
ata cca cat ccc gca ggg tta aag aag aaa aaa tca gta aca gta ctg	624
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu	
195 200 205	
gat gtg ggt gat gca tat ttt tca att ccc tta tgt gaa gac ttc aga	672
Asp Val Gly Asp Ala Tyr Phe Ser Ile Pro Leu Cys Glu Asp Phe Arg	
210 215 220	
aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg	720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly	
225 230 235 240	
att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca	768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
cag aat cca gaa atg gtc atc tat caa tac gtg gat gat ttg tat gta	864
Gln Asn Pro Glu Met Val Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val	
275 280 285	
gga tct gac tta gaa ata gag cag cat aga aca aaa ata gat gaa ctg	912
Gly Ser Asp Leu Glu Ile Glu Gln His Arg Thr Lys Ile Asp Glu Leu	
290 295 300	
aga caa tat ctg tgg aag tgg gga ttt tac aca cca gac aaa aaa cat	960
Arg Gln Tyr Leu Trp Lys Trp Gly Phe Tyr Thr Pro Asp Lys Lys His	
305 310 315 320	
cag aca gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Thr Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act	1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	



			180				185				190							
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aaa	aag	tca	gta	aca	gta	ctg	624		
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu			
			195				200				205							
gat	gtg	ggg	gat	gca	tat	ttt	tca	gtt	ccc	tta	gat	aaa	gac	ttc	agg	672		
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Lys	Asp	Phe	Arg			
			210				215				220							
aag	tac	act	gca	ttt	act	ata	cct	agt	ata	aac	aat	gag	aca	cca	ggg	720		
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly			
			225				230				235				240			
att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768		
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro			
			245				250				255							
gca	ata	ttc	caa	agt	agc	atg	ata	aaa	atc	tta	gag	cct	ttc	aga	aaa	816		
Ala	Ile	Phe	Gln	Ser	Ser	Met	Ile	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys			
			260				265				270							
caa	aat	cca	gac	atg	gtc	atc	tat	caa	tac	atg	gat	gat	ttg	tat	gta	864		
Gln	Asn	Pro	Asp	Met	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val			
			275				280				285							
gga	tct	gac	tta	gaa	ata	gga	cag	cac	aga	aca	aaa	ata	gag	gaa	ctg	912		
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu			
			290				295				300							
aga	caa	cat	ctg	ttg	aag	tgg	gga	ttt	acc	aca	cca	gac	aag	aaa	cat	960		
Arg	Gln	His	Leu	Leu	Lys	Trp	Gly	Phe	Thr	Thr	Pro	Asp	Lys	Lys	His			
			305				310				315				320			
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggt	tat	gaa	ctc	cat	cct	gat	1008		
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp			
			325				330				335							
aaa	tgg	aca	gta	cag	cct	ata	aag	ctg	cca	gaa	aaa	gac	agc	tgg	act	1056		
Lys	Trp	Thr	Val	Gln	Pro	Ile	Lys	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr			
			340				345				350							
gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	tta	aat	tgg	gca	agt	cag	1104		
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Ser	Gln			
			355				360				365							
att	tac	cca	ggg													1116		
Ile	Tyr	Pro	Gly															
			370															

```
<210> 7
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

```
<220>
<221> CDS
<222> (0) ... (297)
<223> HIV Protease
```

```
<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 7  
cct cag atc act ctt tgg caa cga ccc ctt gtc aca ata aar ata ggg 48

Pro 1	Gln	Ile	Thr	Leu 5	Trp	Gln	Arg	Pro	Leu 10	Val	Thr	Ile	Lys	Ile 15	Gly	
ggg Gly	caa Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96
tta Leu	gag Glu	gaa Glu 35	atn Xaa	aat Asn	tta Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	ggg Gly	144
gga Gly	att Ile 50	gga Gly	ggg Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ctt Leu	gta Val	192
gaa Glu 65	aty Xaa	tgt Cys	gga Gly	cat His	aar Lys 70	gct Ala	ata Ile	ggg Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
ccc Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	caa Gln	att Ile	ggg Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
ccg Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	ccc Pro	aaa Lys	gtt Val 120	aaa Lys	cat His	ggc Gly	cct Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aag Lys	cct Pro	tta Leu	gtt Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu 140	atg Met	gga Gly	aaa Lys	gaa Glu	ggg Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aaa Lys	aga Arg	act Thr	caa Gln	gac Asp 185	tty Phe	tgg Trp	gaa Glu	gtc Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	tca Ser	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggg Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	ttg Leu	gat Asp 220	gaa Glu	gac Asp	tta Leu	gag Glu	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816

caa aat cca gac ata gtt atc tat caa tac atg gat gat ttg tat gta Gln Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285	864
gga tca gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912
aga caa cat ctg ttg ggg tgg ggg ttt acc aca cca gac aaa aaa cat Arg Gln His Leu Leu Gly Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335	1008
aaa tgg aca gta cag cct ata gtg ctg cca aca aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Thr Lys Asp Ser Trp Thr 340 345 350	1056
gtc aat gac ata cag aag tta gtg gga aaa ttg aac tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365	1104
att tat gca ggg Ile Tyr Ala Gly 370	1116
 <210> 8 <211> 1116 <212> DNA <213> Human Immunodeficiency Virus (HIV)	
 <220> <221> CDS <222> (0)...(297) <223> HIV Protease	
 <221> CDS <222> (298)...(1116) <223> Portion of HIV Reverse Transcriptase	
 <400> 8	
cct cag atc act ctt tgg caa cga ccc cty gtc aca gta aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Val Lys Ile Gly 1 5 10 15	48
ggg caa ata aag gaa gct yta tta gat aca gga gca gat gat aca gta Gly Gln Ile Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa ata ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Pro Ile 50 55 60	192
gaa atc tgt gga caa aaa gct ata agt aca gta tta gta gga cct aca Glu Ile Cys Gly Gln Lys Ala Ile Ser Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aat ata att gga aga aat ctg atg act cag att ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr 85 90 95	288

tta aat ttt cct att agt cct att gaa act gta cca gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa	384
Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta gta gaa atc tgt aca gaa atg gaa aag gaa ggg	432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly	
130 135 140	
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt	480
Lys Ile Ser Lys Ile Glu Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe	
145 150 155 160	
gcc ata aag aaa aaa ggc agt aac aga tgg aga aaa tta gta gat ttc	528
Ala Ile Lys Lys Lys Gly Ser Asn Arg Trp Arg Lys Leu Val Asp Phe	
165 170 175	
aga gaa ctt aat aag aaa act caa gac ttc tgg gaa gtt caa tta gga	576
Arg Glu Leu Asn Lys Lys Thr Gln Asp Phe Trp Glu Val Gln Leu Gly	
180 185 190	
ata cca cat ccc gca ggg cta aaa aag aaa aaa tca gta aca gta ctg	624
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu	
195 200 205	
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gaa ttc agg	672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Glu Phe Arg	
210 215 220	
aag tat act gca ttt acc ata cct agt aca aac aat gag aca cca ggg	720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Thr Asn Asn Glu Thr Pro Gly	
225 230 235 240	
att aga tat cag tac aat gtg ctt cca caa gga tgg aaa ggg tca cca	768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
caa aat cca gac ata gtt atc tat caa tac atg gat gat ttg tat gta	864
Gln Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val	
275 280 285	
agc tct gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa cta	912
Ser Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu	
290 295 300	
aga caa cat ctg ttg agg tgg gga tta acc aca cca gac aaa aaa cat	960
Arg Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His	
305 310 315 320	
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag cct ata gtg ctg cca gar aaa gac agc tgg act	1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt caa	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	



```

355          360          365
att tac cca ggg
ile Tyr Pro Gly
370

<210> 9
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase

<400> 9
cct cag atc act ctt tgg caa cga ccc cty gtc aaa gta aag ata ggg      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Lys Val Lys Ile Gly
1 5 10 15

ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta      96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
20 25 30

tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atg ata ggg      144
Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly
35 40 45

gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata ccc ata      192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile
50 55 60

gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca      240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr
65 70 75 80

cct gtc aac ata atw gga aga aat ctg ttg act cag att ggt tgc act      288
Pro Val Asn Ile Xaa Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag      336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
100 105 110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa      384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
115 120 125

aaa ata aaa gca tta ata gaa att tgt aca gag atg gag aag gaa ggg      432
Lys Ile Lys Ala Leu Ile Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
130 135 140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt      480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
145 150 155 160

gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc      528
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe
165 170 175

aga gaa ctt aat aag aaa act caa gay ttc tgg gaa gtt car tta gga      576

```



cct cag atc act ctt tgg caa cga ccc ctc gtc aca gta aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Val Lys Ile Gly 1 5 10 15	48
ggg caa ata aag gaa gct yta tta gat aca gga gca gat gat aca gta Gly Gln Ile Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atw ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Xaa Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Pro Ile 50 55 60	192
gaa atc tgt gga caa aaa gct ata agt aca gta tta gta gga cct aca Glu Ile Cys Gly Gln Lys Ala Ile Ser Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aat ata att gga aga aat ctg atg act cag att ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt cct att agt cct att gaa act gta cca gta aaa taa aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys * Lys 100 105 110	336
cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa atc tgt aca gaa atg gaa aag gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155	480
gcc ata aag aaa aaa ggc agt aac aga tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Ser Asn Arg Trp Arg Lys Leu Val Asp Phe 160 165 170 175	528
aga gaa ctt aat aag aaa act caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Lys Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 180 185 190	576
ata cca cat ccc gca ggg cta aaa aag aaa aaa tca gta aca gta ctg Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu 195 200 205	624
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gaa ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Glu Phe Arg 210 215 220	672
aag tat act gca ttt acc ata cct agt aca aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Thr Asn Asn Glu Thr Pro Gly 225 230 235	720
att aga tat cag tac aat gtg ctt ccm caa gga tgg aaa ggg tca cca Ile Arg Tyr Gln Tyr Asn Val Leu Xaa Gln Gly Trp Lys Gly Ser Pro 240 245 250 255	768
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys 260 265 270	816

caa aat cca gac wtr gtt atc tat caa tac atg gat gat ttg tat gta	864
Gln Asn Pro Asp Xaa Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val	
275 280 285	
agc tct gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa cta	912
Ser Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu	
290 295 300	
aga caa cat ctg ttg agg tgg gga tta acc aca cca gac aaa aaa cat	960
Arg Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His	
305 310 315	
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
320 325 330 335	
aaa tgg aca gta cag cct ata gtg ctg cca gag aaa gac agc tgg act	1056
Lys Trp Thr Val Glu Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt caa	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tac cca ggg	1116
Ile Tyr Pro Gly	
370	
<210> 11	
<211> 1116	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1116)	
<223> Portion of HIV Reverse Transcriptase	
<400> 11	
cct cag atc act ctt tgg caa cga ccc aty gtt aca ata aag ata ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Ile Gly	
1 5 10 15	
ggg caa cta aaa raa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Lys Xaa Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atg ata gtg	144
Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Val	
35 40 45	
gga att gga ggt ttt gtc aaa gta aga cag tat gat cag gta ccc ata	192
Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Val Pro Ile	
50 55 60	
gag atc tgt ggg cat aaa att ata ggt aca gta tta ata gga cct acc	240
Glu Ile Cys Gly His Lys Ile Ile Gly Thr Val Leu Ile Gly Pro Thr	
65 70 75 80	
cct gcc aac gta att gga aga aat ctg atg act cag ctt ggt tgc act	288
Pro Ala Asn Val Ile Gly Arg Asn Leu Met Thr Gln Leu Gly Cys Thr	











260										265										270																			
caa	aat	cca	grc	ata	gtt	atc	gtt	caa	tac	gtg	gat	gat	ttg	tat	gta	864																							
Gln	Asn	Pro	Xaa	Ile	Val	Ile	Val	Gln	Tyr	Val	Asp	Asp	Leu	Tyr	Val																								
275										280										285																			
ggg	tct	gac	tta	gaa	ata	ggg	caa	cat	aga	gca	aaa	ata	gag	gag	ttg	912																							
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Ala	Lys	Ile	Glu	Glu	Leu																								
290										300																													
aga	gaa	cat	ctg	ttg	agg	tgg	gga	tty	ttc	aca	cca	gac	gaa	aaa	cat	960																							
Arg	Glu	His	Leu	Leu	Arg	Trp	Gly	Phe	Phe	Thr	Pro	Asp	Glu	Lys	His																								
305										315										320																			
cag	aaa	gaa	cct	cca	ttt	ctt	tgg	atg	ggt	tat	gaa	ctc	cac	cct	gat	1008																							
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp																								
325										335																													
aaa	tgg	acc	gta	cag	cct	ata	aat	ttg	cca	gaa	aaa	gac	agc	tgg	act	1056																							
Lys	Trp	Thr	Val	Gln	Pro	Ile	Asn	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr																								
340										345										350																			
gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	ttg	aat	tgg	gca	agt	cag	1104																							
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Ser	Gln																								
355										360										365																			
att	tac	tca	ggg													1116																							
Ile	Tyr	Ser	Gly																																				
370																																							
<210> 14																																							
<211> 1116																																							
<212> DNA																																							
<213> Human Immunodeficiency Virus (HIV)																																							
<220>																																							
<221> CDS																																							
<222> (0)...(297)																																							
<223> HIV Protease																																							
<221> CDS																																							
<222> (298)...(1116)																																							
<223> Portion of HIV Reverse Transcriptase																																							
<400> 14																																							
cct	caa	atc	act	ctt	tgg	caa	cga	ccc	ctc	gtc	aca	ata	aag	ata	ggg	48																							
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Ile	Lys	Ile	Gly																								
1				5					10					15																									
ggg	caa	gta	agg	gaa	gct	cta	tta	gat	aca	gga	gca	gat	gat	aca	gta	96																							
Gly	Gln	Val	Arg	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val																								
20										25										30																			
tta	gaa	gaa	atg	aat	ttg	cca	gga	aaa	tgg	aag	cca	aaa	atg	ata	ggg	144																							
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Lys	Trp	Lys	Pro	Lys	Met	Ile	Gly																								
35										40										45																			
gga	att	ggg	ggc	ttt	atc	aaa	gta	aga	cag	tat	gat	caa	ata	ccc	ata	192																							
Gly	Ile	Gly	Gly	Phe	Ile	Lys	Val	Arg	Gln	Tyr	Asp	Gln	Ile	Pro	Ile																								
50										55										60																			
gaa	atc	tgt	gga	cat	aaa	gct	ata	ggg	aca	gtg	tta	ata	gga	cct	aca	240																							
Glu	Ile	Cys	Gly	His	Lys	Ala	Ile	Gly	Thr	Val	Leu	Ile	Gly	Pro	Thr																								
65										70										75										80									
cct	gtc	aac	ata	att	gga	aga	aat	ctg	ttg	act	cag	ctt	ggt	tgc	act	288																							



gtc aat gac ata caa aag tta gtg gga aaa tta aat tgg gca agt cag 1104  
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
355 360 365

[illegible]

```
<210> 15
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

```
<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease
```

```
<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

```

<400> 15
cct caa atc act ctt tgg car cga ccc ctc gtt gca ata aag ata ggg      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Ala Ile Lys Ile Gly
      1             5             10             15

```

ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta 96  
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
20 25 30

tta	kaa	gaa	atg	gat	ttg	cca	gga	aga	tgg	aaa	cca	aaa	atg	ata	ggg	144
Leu	Xaa	Glu	Met	Asp	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	
		35					40					45				

gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta tcc wta 192  
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Ser Xaa  
50 55 60

gaa atc tgt gga cat aaa gct ata ggt aca gta tta ata gga cct aca 240  
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr  
65 70 75 80

cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act 288  
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr  
85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
100 105 110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa gga 432  
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly  
130 135 140

aaa att tca aaa att ggg cct gaa aat cca tat aat act cca gta ttt      480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
145                          150                          155                          160

gcc ata aag aaa aaa gac agt act aaa tgg aga aaa ttg gta gat ttc 528  
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
165 170 175

[illegible]

```
<210> 16
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 16																48
cct Pro 1	cag Gln	atc Ile	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ctc Leu 10	gtc Val	aca Thr	ata Ile	aag Lys	ata Ile 15	ggg Gly	
ggg Gly																96
caa Gln	cta Leu	aag Lys 20	gag Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val		
tta Leu																144
gaa Glu	gac Asp 35	atg Met	act Thr	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	ggg Gly		
gga Gly																192
att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ccc Pro	ata Ile		
gaa Glu 65																240
atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80		
cct Pro																288
gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr		
tta Leu																336
aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys		
cca Pro																384
gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu		
aaa Lys																432
ata Ile 130	aaa Lys	gca Ala	tta Leu	rta Xaa	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly		
aag Lys 145																480
att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160		
gcc Ala																528
ata Ile	aag Lys	aaa Lys	aar Lys 165	gat Asp	ggt Gly	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe		
aga Arg																576
gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	att Ile	caa Gln 190	tta Leu	gga Gly		
ata Ile																624
cca Pro	cat His 195	cct Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aag Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu		
gat Asp																672
gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg		
aag Lys 225																720
tat Tyr	act Thr	gca Ala	ttt Phe	act Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240		
att Ile																768
aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro		
gca Ala																816
ata Ile	ttc Phe	caa Gln	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe	aga Arg	aag Lys		

260	265	270	
caa aat cca gac ata gtt atc tat	caa tac atg gat gat ttg tat gta		864
Gln Asn Pro Asp Ile Val Ile Tyr	Gln Tyr Met Asp Asp Leu Tyr Val		
275	280 285		
gga tct gac tta gaa ata ggg cag cat	aga rca aaa ata gag gaa ctg		912
Gly Ser Asp Leu Glu Ile Gly Gln His	Arg Xaa Lys Ile Glu Glu Leu		
290	295 300		
agg caa cat ctg ttg aag tgg gga ttt	acc aca cca gac aaa aaa cat		960
Arg Gln His Leu Leu Lys Trp Gly Phe	Thr Thr Pro Asp Lys Lys His		
305	310 315		
cag aaa gaa cct cca ttc ctt tgg atg	ggg tat gaa ctc cat cca gat		1008
Gln Lys Glu Pro Pro Phe Leu Trp Met	Gly Tyr Glu Leu His Pro Asp		
	325 330 335		
aaa tgg aca gta cag cct ata gtg ctg	cca caa aaa gac agc tgg act		1056
Lys Trp Thr Val Gln Pro Ile Val Leu	Pro Gln Lys Asp Ser Trp Thr		
	340 345 350		
gtc aat gac ata cag aag tta gtg gga	aaa ttg aat tgg gca agt cag		1104
Val Asn Asp Ile Gln Lys Leu Val Gly	Lys Leu Asn Trp Ala Ser Gln		
	355 360 365		
att tat cca ggg			1116
Ile Tyr Pro Gly			
370			
<210> 17			
<211> 1116			
<212> DNA			
<213> Human Immunodeficiency Virus (HIV)			
<220>			
<221> CDS			
<222> (0)...(297)			
<223> HIV Protease			
<221> CDS			
<222> (298)...(1116)			
<223> Portion of HIV Reverse Transcriptase			
<400> 17			
cct caa atc act ctt tgg caa cga ccc	aty gtc aca ata aag gta ggg		48
Pro Gln Ile Thr Leu Trp Gln Arg Pro	Xaa Val Thr Ile Lys Val Gly		
1	5 10 15		
ggg caa cta aag gaa gcc cta ata gat	aca gga gca gat gat aca gtg		96
Gly Gln Leu Lys Glu Ala Leu Ile Asp	Thr Gly Ala Asp Asp Thr Val		
	20 25 30		
tta gaa gaa atg aat ttg cca gga aga	tgg aaa cca aaa ttg ata ggg		144
Leu Glu Glu Met Asn Leu Pro Gly Arg	Trp Lys Pro Lys Leu Ile Gly		
	35 40 45		
gga att gga ggt ttt atc aaa gta aga	cag tat gat cag rta ccc ata		192
Gly Ile Gly Gly Phe Ile Lys Val Arg	Gln Tyr Asp Gln Xaa Pro Ile		
	50 55 60		
gaa atc tgt gga cat aaa gct gta ggt	tca gtg tta gta gga cct aca		240
Glu Ile Cys Gly His Lys Ala Val Gly	Ser Val Leu Val Gly Pro Thr		
	65 70 75 80		
cct gcc aac ata att gga aga aat ctg	ttg act cag att ggt tgc act		288

Pro	Ala	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Ile	Gly	Cys	Thr		
				85					90					95			
cta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336	
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys		
			100					105					110				
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	aaa	gaa	384	
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Lys	Glu		
		115					120					125					
aaa	ata	gaa	gca	tta	gta	gaa	atc	tgt	gca	gaa	ctg	gaa	gag	gca	ggg	432	
Lys	Ile	Glu	Ala	Leu	Val	Glu	Ile	Cys	Ala	Glu	Leu	Glu	Glu	Ala	Gly		
	130					135					140						
aaa	att	tca	aaa	att	ggg	cct	gaa	aat	cca	tac	aat	act	cca	gta	ttt	480	
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe		
	145				150					155					160		
gcc	ata	aag	aar	aag	aac	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528	
Ala	Ile	Lys	Lys	Lys	Asn	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe		
				165					170					175			
aga	gaa	ctt	aac	aag	aga	act	caa	gac	ttc	tgg	gaa	gtt	caa	tta	gga	576	
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly		
			180					185					190				
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	ctg	624	
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu		
		195					200					205					
gat	gtg	ggt	gat	gca	tat	ttc	tca	att	ccc	tta	gat	aag	gac	ttc	agg	672	
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Ile	Pro	Leu	Asp	Lys	Asp	Phe	Arg		
	210					215					220						
aag	tat	act	gca	ttt	aca	ata	cct	agy	ata	aac	aat	gag	aca	cca	ggg	720	
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Xaa	Ile	Asn	Asn	Glu	Thr	Pro	Gly		
	225				230				235						240		
att	aga	tat	cag	tac	aat	gtg	ctt	cma	cag	gga	tgg	aaa	gga	tca	cca	768	
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Xaa	Gln	Gly	Trp	Lys	Gly	Ser	Pro		
			245					250						255			
gca	ata	ttc	cag	tgt	agc	atg	aca	aaa	atc	tta	gat	cct	ttt	aga	aaa	816	
Ala	Ile	Phe	Gln	Cys	Ser	Met	Thr	Lys	Ile	Leu	Asp	Pro	Phe	Arg	Lys		
			260					265					270				
caa	aat	cca	gac	ata	gtt	atc	tat	caa	tac	gtg	gat	gat	ttg	tat	gta	864	
Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Val	Asp	Asp	Leu	Tyr	Val		
		275					280					285					
gga	tct	gac	tta	gaa	ata	ggg	car	cat	aga	aca	aaa	ata	gag	gaa	ctg	912	
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu		
	290					295					300						
aga	caa	yat	ctg	tgg	aag	tgg	gga	ttt	tac	aca	cca	gag	aat	aaa	cat	960	
Arg	Gln	Xaa	Leu	Trp	Lys	Trp	Gly	Phe	Tyr	Thr	Pro	Glu	Asn	Lys	His		
	305				310				315					320			
cag	aaa	gaa	cct	cca	ttc	cwt	tgg	atg	ggt	tat	gaa	ctc	cat	cct	gat	1008	
Gln	Lys	Glu	Pro	Pro	Phe	Xaa	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp		
				325					330					335			
aaa	tgg	aca	gta	cag	cct	ata	gtg	ctg	cca	gaa	aag	gac	agc	tgg	act	1056	
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr		
			340					345					350				

```

gtc aat gac ata cag aaa tta gtg gga aaa ttg aat tgg gca agt cag      1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln
      355                      360                      365

att tat gcg ggg      1116
Ile Tyr Ala Gly
      370

<210> 18
<211> 1117
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1117)
<223> Portion of HIV Reverse Transcriptase

<400> 18
cct caa atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly
      1                      5                      10                      15

ggg car cta aag gaa gct cta tta gat aca gga gca gat gat aca gta      96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
      20                      25                      30

gta gaa gaa atg aat tta tca gga agg tgg aaa cca aaa atg ata ggg      144
Val Glu Glu Met Asn Leu Ser Gly Arg Trp Lys Pro Lys Met Ile Gly
      35                      40                      45

gga att gga ggt ttt atc aaa gta aga saa tat gaa cag ata cct gta      192
Gly Ile Gly Gly Phe Ile Lys Val Arg Xaa Tyr Glu Gln Ile Pro Val
      50                      55                      60

gaa att tgt gga cat aaa gct gta ggt aca gta tta gtg gga cct aca      240
Glu Ile Cys Gly His Lys Ala Val Gly Thr Val Leu Val Gly Pro Thr
      65                      70                      75                      80

cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act      288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
      85                      90                      95

tta aat ttt ccc att agt ccc att gaa act gta cca gta aaa ttg aag      336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
      100                      105                      110

cca gga atg gat ggc ccg aga gtt aaa caa tgg cca ttg aca gaa gaa      384
Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu
      115                      120                      125

aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg      432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
      130                      135                      140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt      480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
      145                      150                      155                      160

gcc ata aag aaa aaa gac agt aat aaa tgg agg aaa tta gtg gat ttc      528
Ala Ile Lys Lys Lys Asp Ser Asn Lys Trp Arg Lys Leu Val Asp Phe
      165                      170                      175

```











```

gtc aat gac ata cag aag ttt agt ggg aaa att gaa ttg ggc aag tca 1104
Val Asn Asp Ile Gln Lys Phe Ser Gly Lys Ile Glu Leu Gly Lys Ser
      355                      360                      365

gat tta tgc agg g
Asp Leu Cys Arg
      370

<210> 21
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase

<400> 21
cct cag atc act ctt tgg caa cga mcc gtt gtc wca ata aag ata ggg 48
Pro Gln Ile Thr Leu Trp Gln Arg Xaa Val Val Xaa Ile Lys Ile Gly
      1                      5                      10                      15

ggg caa cta aaa gaa gct cta tta gay aca ggg gca gat gat aca gta 96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
      20                      25                      30

tta gaa gac atg cat ttg cca ggt aga tgg aaa cca aaa atg ata gtg 144
Leu Glu Asp Met His Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Val
      35                      40                      45

gga att ggg ggt ttt gtc aaa gta aga cag tat gat gat cag ata cct gta 192
Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Ile Pro Val
      50                      55                      60

gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca 240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr
      65                      70                      75                      80

cca gcc aac ata att gga aga aat ctg ttg act cag att ggt tgc act 288
Pro Ala Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
      85                      90                      95

tta aat ttc ccc atc agt cct att gaa act gta cca gta aaa tta aag 336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
      100                      105                      110

cca gga atg gat ggc cca aaa att aga caa tgg cca tta aca gaa gaa 384
Pro Gly Met Asp Gly Pro Lys Ile Arg Gln Trp Pro Leu Thr Glu Glu
      115                      120                      125

aaa ata aaa gca tta gta gaa atc tgt aca gaa atg gaa aag gaa ggg 432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
      130                      135                      140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt 480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
      145                      150                      155                      160

gcc ata aag aaa aaa aat agt act aaa tgg aga aaa tta gta gat ttc 528
Ala Ile Lys Lys Lys Asn Ser Thr Lys Trp Arg Lys Leu Val Asp Phe
      165                      170                      175

```











```

gtt aat gac ata cag aaa tta gtt gga aaa ttg aat tgg gca agt caa 1104
Xaa Asn Asp Ile Gln Lys Leu Xaa Gly Lys Leu Asn Trp Ala Ser Gln
      355      360      365

att tac cca ggg 1116
Ile Tyr Pro Gly
      370

<210> 24
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase

<400> 24
cct cag atc act ctt tgg caa cga ccc ata gtc aca ata aag ata ggg 48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly
      1      5      10      15

ggg caa cta aag gaa gct cta ata gat aca gga gca gat gat aca gta 96
Gly Gln Leu Lys Glu Ala Leu Ile Asp Thr Gly Ala Asp Asp Thr Val
      20      25      30

tta gaa gac ata aat ttg cca gga aga tgg aaa cca aaa tta ata ggg 144
Leu Glu Asp Ile Asn Leu Pro Gly Arg Trp Lys Pro Lys Leu Ile Gly
      35      40      45

gga att gga ggt ttt gtc aga gtg aaa cag tat gat cag ata ccc ata 192
Gly Ile Gly Gly Phe Val Arg Val Lys Gln Tyr Asp Gln Ile Pro Ile
      50      55      60

gaa att tgt gga cat aaa gtt ata ggt aca gta tta gta gga cct aca 240
Glu Ile Cys Gly His Lys Val Ile Gly Thr Val Leu Val Gly Pro Thr
      65      70      75      80

cct gcc aac ata att gga aga aat ctg ttg act cag att ggt tgc act 288
Pro Ala Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
      85      90      95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
      100      105      110

cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa 384
Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu
      115      120      125

aaa ata aaa gca tta aca gaa atc tgt wca gag atg gaa aag gaa ggg 432
Lys Ile Lys Ala Leu Thr Glu Ile Cys Xaa Glu Met Glu Lys Glu Gly
      130      135      140

aaa att tca aaa att ggg cct gaa aat cca tac aac act cca gta ttt 480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
      145      150      155      160

gcy ata cac aag aaa aat agt aat aga tgg aga aaa gta gta gat ttc 528
Xaa Ile His Lys Lys Asn Ser Asn Arg Trp Arg Lys Val Val Asp Phe
      165      170      175

```

agg gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga	576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly	
180 185 190	
ata cca cat ccc gca gga tta aaa aag aac aaa tca gta aca gta ctg	624
Ile Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu	
195 200 205	
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aag gat ttc agg	672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg	
210 215 220	
aag tat act gcg ttt acc ata cct agt ata aac aat gag aca cca ggg	720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly	
225 230 235 240	
atc aga tac cag tac aat gtg ctt cca caa gga tgg aaa gga tca cca	768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg aca aga atc tta gag cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Arg Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
caa aat cca gaa ata gtt atc tgt caa tac atg gat gat ttg tat gta	864
Gln Asn Pro Glu Ile Val Ile Cys Gln Tyr Met Asp Asp Leu Tyr Val	
275 280 285	
gga tct gac tta gaa ata ggg cag cat aga aca aaa ata aak gaa ctg	912
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Xaa Glu Leu	
290 295 300	
aga saa cat ctg ttg agg tgg gga ttt ttc aca cca gac caa aaa cat	960
Arg Xaa His Leu Leu Arg Trp Gly Phe Phe Thr Pro Asp Gln Lys His	
305 310 315 320	
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag cct ata gtg ctg cca gaa aar gac agt tgg acw	1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Xaa	
340 345 350	
gty aat gac ata cag aaa tta gtk gga aaa ttg aat tgg gca agt caa	1104
Xaa Asn Asp Ile Gln Lys Leu Xaa Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tac cca ggg	1116
Ile Tyr Pro Gly	
370	

<210> 25  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400> 25	
cct caa atc act ctt tgg caa cga ccc ctc gtc aca ata aaa ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly 1 5 10 15	48
ggg caa cta aag gaa gct cta cta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg agt ttg cca gga aaa tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Ser Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta tcc atg Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Ser Met 50 55 60	192
gaa atc tgt gga cat aaa gtt ata ggt aca gta tta gta gga tct aca Glu Ile Cys Gly His Lys Val Ile Gly Thr Val Leu Val Gly Ser Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ytg ttg act cag ctt ggg tgc act Pro Val Asn Ile Ile Gly Arg Asn Xaa Leu Thr Gln Leu Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta ata gaa att tgt aca gaa atg gaa aag gar ggg Lys Ile Lys Ala Leu Ile Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480
gcc ata aag aaa aaa gac agt act aaa tgg aga aag tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 170 175	528
aga gaa ctt aat aag aaa act caa gat ttc tgg gaa rtt caa tta gga Arg Glu Leu Asn Lys Lys Thr Gln Asp Phe Trp Glu Xaa Gln Leu Gly 180 185 190	576
ata cca cat ccc gca ggg tta caa aag aac aaa tca gta aca gta ctg Ile Pro His Pro Ala Gly Leu Gln Lys Asn Lys Ser Val Thr Val Leu 195 200 205	624
gat gtg ggt gat gca tat ttt tca gtc ccc tta gat aaa gac ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg 210 215 220	672
aag tat act gca ttt acc ata cct agt aca aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Thr Asn Asn Glu Thr Pro Gly 225 230 235 240	720
att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttc caa tat agc atg aca aaa atc tta gag cct ttt aga aaa Ala Ile Phe Gln Tyr Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	816





gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag 1104  
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
355 360 365

att tac cca ggg 1116  
Ile Tyr Pro Gly  
370

<210> 27  
<211> 1113  
<212> DNA  
<213> Human Immunodeficiency Virus (HIV)

<220>  
<221> CDS  
<222> (0)...(297)  
<223> HIV Protease

<221> CDS  
<222> (298)...(1116)  
<223> Portion of HIV Reverse Transcriptase

<400> 27  
cct cag atc act ctt tgg caa cga ccc atc gtc gaa ata aag gta ggg 48  
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Glu Ile Lys Val Gly  
1 5 10 15

ggg caa cta ata gaa gct cta tta gat aca gga gca gat gat aca gta 96  
Gly Gln Leu Ile Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
20 25 30

tta gaa gaa ata aat tta cca gga aga tgg aaa cca aga atg ata ggg 144  
Leu Glu Glu Ile Asn Leu Pro Gly Arg Trp Lys Pro Arg Met Ile Gly  
35 40 45

gga att gga ggt ttt gtc aaa gta aga cag tat gat cag gta cct atc 192  
Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Val Pro Ile  
50 55 60

gaa atc tgt gga cat aaa gtt ata agt aca gta tta gta gga cct aca 240  
Glu Ile Cys Gly His Lys Val Ile Ser Thr Val Leu Val Gly Pro Thr  
65 70 75 80

cct gcc aac ata att gga aga aat ctg atg act cag att ggt tgc act 288  
Pro Ala Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr  
85 90 95

tta aat ttt cct att agt cct att gaa act gta cca gta aaa tta aaa 336  
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
100 105 110

cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa 384  
Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu  
115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa ytg gaa gag gaa ggg 432  
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Xaa Glu Glu Glu Gly  
130 135 140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca ata ttt 480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe  
145 150 155 160

gcc ata aag aag aaa agt ggt aga tgg aga aaa ata gta gat ttt aga 528  
Ala Ile Lys Lys Lys Ser Gly Arg Trp Arg Lys Ile Val Asp Phe Arg  
165 170 175

gaa ctt aat aag aga act caa gat ttc tgg gaa gtt caa tta gga ata	576
Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile	
180 185 190	
cca cat ccc gca ggg tta aaa aag aac aag tca gta aca att ctg gat	624
Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Val Thr Ile Leu Asp	
195 200 205	
gtg ggt gat gca tat ttt tca gtt ccc tta gat aag gaa ttc agg aag	672
Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Glu Phe Arg Lys	
210 215 220	
tat act gca ttt acc ata cct agt ata aat aat gag aca cca ggg att	720
Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile	
225 230 235 240	
aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca gca	768
Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala	
245 250 255	
ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa caa	816
Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln	
260 265 270	
aat cca gac ata gtt atc tat cag tac gtg gat gat ttg tat gta gga	864
Asn Pro Asp Ile Val Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val Gly	
275 280 285	
tct gat tta gaa ata ggg gag cat aga aca aaa ata gag gaa ctg aga	912
Ser Asp Leu Glu Ile Gly Glu His Arg Thr Lys Ile Glu Glu Leu Arg	
290 295 300	
car cat ctg tta arg tgg gga ttt ttc aca cca gaa caa aaa cat cag	960
Gln His Leu Leu Xaa Trp Gly Phe Phe Thr Pro Glu Gln Lys His Gln	
305 310 315 320	
aaa gaa cct ccm ttc cak tgg atg ggt tat gaa ctc cay cct gat aaa	1008
Lys Glu Pro Xaa Phe Xaa Trp Met Gly Tyr Glu Leu His Pro Asp Lys	
325 330 335	
tgg aca gta cas cct ata gtg ctg cca gaa aaa gat agc tgg act gtc	1056
Trp Thr Val Xaa Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val	
340 345 350	
aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag att	1104
Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile	
355 360 365	
tac cca ggg	1113
Tyr Pro Gly	
370	

<210> 28  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase













<400> 31	
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly 1 5 10 15	48
ggg caa tta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
cta gaa gac gtg cat ttg cca gga aaa tgg aaa cca aaa atg ata ggg Leu Glu Asp Val His Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat gag gta ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Glu Val Pro Ile 50 55 60	192
gaa ctc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca Glu Leu Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
ccc gtc aac ata att gga aga aat ctg wtg act caa ctt ggg tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Xaa Thr Gln Leu Gly Cys Thr 85 90 95	288
cta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432
aaa att tca aga gtt ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Arg Val Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480
gyc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc Xaa Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 170 175	528
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 180 185 190	576
ata cca cay ccc gca ggg tta aaa aag aaa aaa tca gta aca gta ctr Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Xaa 195 200 205	624
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gaa ttc aga Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Glu Phe Arg 210 215 220	672
aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly 225 230 235 240	720
att aga tac cag tac aat gtg ctt cca caa gga tgg aaa gga tca cca Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttc caa agt agc atg aca aaa atc tta gat cct ttt agg aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Asp Pro Phe Arg Lys	816

260	265	270	
caa aac cca gac ata gtt atc tat	caa tac gtg gat gat	ttg tat gta	864
Gln Asn Pro Asp Ile Val Ile Tyr	Gln Tyr Val Asp Asp	Leu Tyr Val	
275	280	285	
gga tcy gac tta gaa ata gga cag cat agr rca aaa ata gaa gaa ctg			912
Gly Xaa Asp Leu Glu Ile Gly Gln His Xaa Xaa Lys Ile Glu Glu Leu			
290	295	300	
aga caa cat ctg ttg aag tgg gga ttt acc aca cca gac aag aaa cat			960
Arg Gln His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His			
305	310	315	320
car aaa gaa cct cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat			1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			
325	330	335	
aaa tgg aca gtg cag cct ata gtg ctg cca gaa aag gac agc tgg act			1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr			
340	345	350	
gtc aat gac ant aca gaa gtt agt ggg aaa att gaa ttg ggc aag tca			1104
Val Asn Asp Xaa Thr Glu Val Ser Gly Lys Ile Glu Leu Gly Lys Ser			
355	360	365	
gat tta tgc agg g			1117
Asp Leu Cys Arg			
370			
<210> 32			
<211> 1116			
<212> DNA			
<213> Human Immunodeficiency Virus (HIV)			
<220>			
<221> CDS			
<222> (0)...(297)			
<223> HIV Protease			
<221> CDS			
<222> (298)...(1116)			
<223> Portion of HIV Reverse Transcriptase			
<400> 32			
cct caa atc act ctt tgg caa cga ccc cty gtc gca ata agg ata ggg			48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Ala Ile Arg Ile Gly			
1	5	10	15
ggg caa cta aag gaa gcc cta tta gat aca gga gca gat gat aca gta			96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val			
20	25	30	
tta gaa gac atg gag ttg cca gga aga tgg aag cca aaa atg ata ggg			144
Leu Glu Asp Met Glu Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly			
35	40	45	
gga att gga ggt ttt atc aaa gta aam cag tat gat cag ata ctt gta			192
Gly Ile Gly Gly Phe Ile Lys Val Xaa Gln Tyr Asp Gln Ile Leu Val			
50	55	60	
gaa atc tgt gga cat aaa gct gta ggt aca gta tta ata gga cct aca			240
Glu Ile Cys Gly His Lys Ala Val Gly Thr Val Leu Ile Gly Pro Thr			
65	70	75	80
cct gtc aac ata att gga aga aat ttg ttg act cag att ggc tgc act			288





```

gtc aat gac ata cag aar tta gtg gga aaa ttg aat tgg gca agt cag      1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln
      355                                360                                365

att tac cca ggg
Ile Tyr Pro Gly
      370

<210> 33
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase

<400> 33
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly
      1                                5                                10                                15

ggg caa cta aag gaa gct cta tta kat aca gga gca gat gat aca gtm      96
Gly Gln Leu Lys Glu Ala Leu Leu Xaa Thr Gly Ala Asp Asp Thr Xaa
      20                                25                                30

tta gaa gac atg act ttg cca gga aga tgg aaa cca aaa atg ata ggg      144
Leu Glu Asp Met Thr Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly
      35                                40                                45

gga att gga ggt ttt atc aaa gta aaa cag tat gag gag ata ccc ata      192
Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Glu Glu Ile Pro Ile
      50                                55                                60

gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca      240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr
      65                                70                                75                                80

cct gtc aac ata att gga aga aat ttg ttg act cag att ggt tgc act      288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
      85                                90                                95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aaa      336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
      100                                105                                110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa      384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
      115                                120                                125

aaa ata aaa gca ttw gta gaa att tgt gca gaa ctg gaa aag gaa ggg      432
Lys Ile Lys Ala Xaa Val Glu Ile Cys Ala Glu Leu Glu Lys Glu Gly
      130                                135                                140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt      480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
      145                                150                                155                                160

gcc ata aag aaa aaa gac ggt act aaa tgg aga aag gta aca gat ttt      528
Ala Ile Lys Lys Lys Asp Gly Thr Lys Trp Arg Lys Val Thr Asp Phe
      165                                170                                175

```

aga gaa ctt aat aag agg ach caa gac ttc tgg gaa gtt caa tta gga 576  
 Arg Glu Leu Asn Lys Arg Xaa Gln Asp Phe Trp Glu Val Gln Leu Gly  
 180 185 190

ata cca cat ccc tca ggg tta aaa aag aaa aaa tca gta aca gta ctg 624  
 Ile Pro His Pro Ser Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu  
 195 200 205

gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg 672  
 Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg  
 210 215 220

aag tat act gca ttt acc ata cct agt ata aac aat gcg aca cca ggg 720  
 Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Ala Thr Pro Gly  
 225 230 235 240

att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca 768  
 Ile Arg Tyr Gln Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro  
 245 250 255

gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa 816  
 Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys  
 260 265 270

caa aat cca gac atg gtt atc tat caa tac atg gat gat ttg tat gta 864  
 Gln Asn Pro Asp Met Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val  
 275 280 285

gga tct gat tta gaa ata ggg cag cat aga aca aaa ata gag gaa ctg 912  
 Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu  
 290 295 300

aga caa cat ctg ttg aag tgg ggt ttt acc aca cca gac aaa aaa cat 960  
 Arg Gln His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His  
 305 310 315 320

cag aaa gaa cct cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat 1008  
 Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp  
 325 330 335

aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act 1056  
 Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr  
 340 345 350

gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag 1104  
 Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
 355 360 365

att tat tca ggg 1116  
 Ile Tyr Ser Gly  
 370

<210> 34  
 <211> 1119  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1119)  
 <223> Portion of HIV Reverse Transcriptase

<400> 34	
cct cag atc act ctt tgg caa cga ccc atc gtc aca ata aag ata ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly 1 5 10 15	48
ggg cag cta aag gaa gct cta ttr gac aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Xaa Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa ata ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly 35 40 45	144
gga att gga ggt ttt att aaa gta aaa cag tat gaa cag ata acc ata Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Gln Ile Thr Ile 50 55 60	192
gam atc tgt gga cat aaa gct aca ggt aca gta tta gta gga cct aca Xaa Ile Cys Gly His Lys Ala Thr Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac gta att gga aga aat atg atg act cag att ggt tgc act Pro Val Asn Val Ile Gly Arg Asn Met Met Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gaa aag gaa ggg Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly 130 135 140	432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480
gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 170 175	528
aga gaa ctt aac aag aga act caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 180 185 190	576
ata cca cat ccc gca ggg tta cca aag aac aaa tca gta acg gta ctg Ile Pro His Pro Ala Gly Leu Pro Lys Asn Lys Ser Val Thr Val Leu 195 200 205	624
gat gtg ggt gat gca tat ttt tca gtt cct tta gat gaa gac ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg 210 215 220	672
aag tac act gca ttt acc ata cct agg tat aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Arg Tyr Asn Asn Glu Thr Pro Gly 225 230 235 240	720
act aga tat cag tac aat gtg ctt cct atg gga tgg aaa gga tca cca Thr Arg Tyr Gln Tyr Asn Val Leu Pro Met Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aga Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Arg	816



Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Leu	Gly	Cys	Thr	
				85					90					95		
cta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gaa	att	tgt	aca	gaa	atg	gaa	aag	gaa	gga	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly	
	130					135					140					
aaa	att	tca	aaa	att	gga	cct	gaa	aat	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aag	gac	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asp	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aag	aga	act	caa	gac	ttt	tgg	gaa	gtc	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	tta	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu	
		195					200					205				
gat	gtg	gga	gat	gca	tat	ttt	tca	gtt	ccc	tta	gat	aaa	gac	ttc	agg	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Lys	Asp	Phe	Arg	
	210					215					220					
aag	tat	act	gca	ttt	acc	ata	cct	agt	ata	aac	aat	gag	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
			245						250					255		
gca	ata	ttc	caa	agt	agc	atg	aca	aaa	atc	tta	gag	cct	ttt	aga	aag	816
Ala	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			
caa	aat	cca	gac	ata	gtc	ata	tat	caa	tac	atg	gat	gat	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
		275					280					285				
ggg	tct	gac	tta	gaa	ata	gga	cag	cat	aga	aca	aaa	ata	gag	gaa	ctg	912
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu	
	290					295					300					
aga	caa	cac	ttg	ttg	maa	tgg	gga	ttc	acc	aca	cca	gac	aaa	aag	cat	960
Arg	Gln	His	Leu	Leu	Xaa	Trp	Gly	Phe	Thr	Thr	Pro	Asp	Lys	Lys	His	
	305				310					315					320	
cag	aaa	gaa	ccc	cca	ttc	ctt	tgg	atg	ggt	tat	gaa	ctc	cat	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
				325					330					335		
aaa	tgg	aca	gta	cag	cct	ata	kaa	ctg	cca	gaa	aaa	gac	agc	tgg	ctg	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Xaa	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Leu	
			340					345					350			





```

<400> 37
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aaa ata ggg      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly
  1          5          10          15

ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta      96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
          20          25          30

tta gaa gac atg aat ttg cca gga aga tgg aaa cca aaa atg ata ggg      144
Leu Glu Asp Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly
          35          40          45

gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta ccc ata      192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Pro Ile
          50          55          60

gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca      240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr
  65          70          75          80

cct gtc aac ata att gga aga aat ctg atg aca cag ctt ggt tgt act      288
Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Leu Gly Cys Thr
          85          90          95

tta aat ttt cct att agt cct att gaa act gta cca gta aaa tta aag      336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
          100          105          110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa      384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
          115          120          125

aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg      432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
          130          135          140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt      480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
          145          150          155          160

gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc      528
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe
          165          170          175

agg gaa ctt aat aag aaa act caa gac ttc tgg gaa gtt caa tta ggg      576
Arg Glu Leu Asn Lys Lys Thr Gln Asp Phe Trp Glu Val Gln Leu Gly
          180          185          190

ata cca cat cct gca gga tta aaa aag aat aaa tca gta aca gta ctg      624
Ile Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu
          195          200          205

gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg      672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg
          210          215          220

aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg      720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly
          225          230          235          240

att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca      768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro
          245          250          255

gca ata ttc caa agt agc atg aca aaa att tta gat cct ttt aga aaa      816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Asp Pro Phe Arg Lys

```



260	265	270	
cag aat cca gat ata gtt atc tat caa tac atg gat gat ttg tat gta Gln Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285			864
gga tct gac tta gag ata ggg cag cat aga gca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Ala Lys Ile Glu Glu Leu 290 295 300			912
aga gca cat ctg ttg aag tgg gga ttt acc acc cca gac aaa aaa cat Arg Ala His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320			960
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335			1008
aaa tgg aca gta cag cct ata gtg ctg cca gaa aag gac agc tgg act Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350			1056
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365			1104
att tac gca ggg Ile Tyr Ala Gly 370			1116
 <210> 38 <211> 1117 <212> DNA <213> Human Immunodeficiency Virus (HIV)			
 <220> <221> CDS <222> (0)...(297) <223> HIV Protease			
 <221> CDS <222> (298)...(1117) <223> Portion of HIV Reverse Transcriptase			
 <400> 38			
cct caa tca ctt ctt tgg caa cga ccc mtc gtc aca ata aag gta ggg Pro Gln Ser Leu Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Val Gly 1 5 10 15			48
ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca ata Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Ile 20 25 30			96
tta gaa gac aya rat ttg cca ggg aga tgg aaa cca aaa ata ata ggg Leu Glu Asp Xaa Xaa Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly 35 40 45			144
gga att gga ggt ttt atc aga gta aga cag tat gat cag gta ccc ata Gly Ile Gly Gly Phe Ile Arg Val Arg Gln Tyr Asp Gln Val Pro Ile 50 55 60			192
gaa atc tgt gga cat aaa gtt gta agt aca gta tta gta gga cct aca Glu Ile Cys Gly His Lys Val Val Ser Thr Val Leu Val Gly Pro Thr 65 70 75 80			240
cct gcc aac ata att gga aga aat ctg atg act cag att ggt tgc act			288

Pro	Ala	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Met	Thr	Gln	Ile	Gly	Cys	Thr	
				85					90					95		
tta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gaa	att	tgt	gaa	gaa	ttg	gaa	aag	gat	ggg	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Glu	Glu	Leu	Glu	Lys	Asp	Gly	
	130					135					140					
aaa	att	tca	aaa	att	ggg	cct	gaa	aat	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aag	aac	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asn	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aag	aga	act	caa	gac	ttc	tgg	gaa	gtt	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	cct	gca	gga	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu	
		195					200					205				
gat	gtg	ggg	gat	gca	tat	ttt	tca	att	ccc	tta	gat	gaa	gac	ttc	aga	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Ile	Pro	Leu	Asp	Glu	Asp	Phe	Arg	
	210					215					220					
aag	tat	act	gca	ttt	acc	ata	cct	agt	ata	aac	aat	gag	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
				245					250					255		
tca	ata	ttc	caa	agt	agc	atg	aca	aaa	atc	tta	gag	cct	ttt	aga	aaa	816
Ser	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			
caa	aat	cca	gac	ata	gtc	atc	tat	caa	tat	atg	gat	gat	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
		275					280					285				
gga	tct	gac	tta	gag	ata	ggg	cag	cat	aga	aca	aaa	ata	gag	gaa	ctg	912
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu	
	290					295					300					
aga	cag	cat	ctg	tgg	aag	tgg	ggg	ttt	tac	aca	cca	gac	ara	aaa	cat	960
Arg	Gln	His	Leu	Trp	Lys	Trp	Gly	Phe	Tyr	Thr	Pro	Asp	Xaa	Lys	His	
	305				310					315					320	
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gac	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
				325					330					335		
aaa	tgg	aca	gta	cag	cct	ata	gtg	ctg	cca	gaa	aag	gac	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr	
			340					345					350			







260	265	270	
caa aat cca gat ata gtt atc tat	caa tac atg gat gat cta tat gta		864
Gln Asn Pro Asp Ile Val Ile Tyr	Gln Tyr Met Asp Asp Leu Tyr Val		
275	280 285		
gga tct gac tta gaa ata gaa cag cat	aga aca aaa ata gag gaa ctg		912
Gly Ser Asp Leu Glu Ile Glu Gln His	Arg Thr Lys Ile Glu Glu Leu		
290	295 300		
aga caa cat ctg ttg agg tgg ggg ttt	acc acc cca gac aaa aaa cat		960
Arg Gln His Leu Leu Arg Trp Gly Phe	Thr Thr Pro Asp Lys Lys His		
305	310 315		
cag aaa gaa ccc cca ttc ctt tgg atg	ggt tat gaa ctc cat cct gat		1008
Gln Lys Glu Pro Pro Phe Leu Trp Met	Gly Tyr Glu Leu His Pro Asp		
325	330 335		
aaa tgg aca gta cag cct ata gtg ctg	cca gaa aaa gac agc tgg act		1056
Lys Trp Thr Val Gln Pro Ile Val Leu	Pro Glu Lys Asp Ser Trp Thr		
340	345 350		
gtc aat gac nat aca aaa gtt agt ggg	gaa aat tga att ggg sca agt		1104
Val Asn Asp Xaa Thr Lys Val Ser Gly	Glu Asn * Ile Gly Xaa Ser		
355	360 365		
cag att tat tgg agg g			1120
Gln Ile Tyr Trp Arg			
370			
<210> 41			
<211> 1059			
<212> DNA			
<213> Human Immunodeficiency Virus (HIV)			
<220>			
<221> CDS			
<222> (0)...(297)			
<223> HIV Protease			
<221> CDS			
<222> (298)...(1059)			
<223> Portion of HIV Reverse Transcriptase			
<400> 41			
cct caa atc act ctt tgg cag cga ccc	ggt gtc aca ata aac ata ggg		48
Pro Gln Ile Thr Leu Trp Gln Arg Pro	Val Val Thr Ile Asn Ile Gly		
1	5 10 15		
ggg caa cta aag gaa gct cta tta gac	aca gga gca gat gat aca gta		96
Gly Gln Leu Lys Glu Ala Leu Leu Asp	Thr Gly Ala Asp Asp Thr Val		
20	25 30		
tta gaa gaa atg aat ttg cca gga aga	tgg aaa cca aaa atg ata ggg		144
Leu Glu Glu Met Asn Leu Pro Gly Arg	Trp Lys Pro Lys Met Ile Gly		
35	40 45		
gga att gga ggt ttt atc aaa gta aga	cag tat gat cag ata ccc ata		192
Gly Ile Gly Gly Phe Ile Lys Val Arg	Gln Tyr Asp Gln Ile Pro Ile		
50	55 60		
gaa atc tgt gga cat aaa act ata ggt	aca gta tta ata gga cct aca		240
Glu Ile Cys Gly His Lys Thr Ile Gly	Thr Val Leu Ile Gly Pro Thr		
65	70 75 80		
cct gtc aac ata att gga aga aat ctg	ttg act cag att ggc tgc act		288

Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Ile	Gly	Cys	Thr	
				85					90					95		
tta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	ata	gaa	att	tgt	aca	gaa	atg	gaa	aag	gaa	ggg	432
Lys	Ile	Lys	Ala	Leu	Ile	Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly	
	130					135					140					
aaa	att	tca	aaa	att	ggg	cct	gaa	aac	ccg	tac	aat	act	cca	gtc	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aaa	gat	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asp	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aac	aag	aaa	act	caa	gac	ttc	tgg	gaa	att	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Lys	Thr	Gln	Asp	Phe	Trp	Glu	Ile	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu		
		195					200					205				
gat	gtg	ggg	gat	gca	tat	ttc	tca	gtt	cct	tta	gat	aaa	gac	ttc	agg	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Lys	Asp	Phe	Arg	
	210					215					220					
aag	tat	act	gca	ttt	acc	ata	cct	agt	aca	aac	aat	gag	acg	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Thr	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
			245						250					255		
gcc	ata	nnn	nnn	nnn	nnn	nnn	nnn	nnn	nnn	nnn	nnn	nnn	nnn	nnn	nnn	816
Ala	Ile	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	
			260					265					270			
nnn	nnn	nnn	nnn	nnn	nnn	nnn	tat	caa	tac	atg	gat	gat	ttg	tat	gta	864
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
			275				280					285				
gga	tct	gac	tta	gaa	ata	gag	cag	cat	aga	aca	aaa	ata	gag	aaa	ctg	912
Gly	Ser	Asp	Leu	Glu	Ile	Glu	Gln	His	Arg	Thr	Lys	Ile	Glu	Lys	Leu	
	290					295					300					
aga	caa	cat	ctg	ttg	agg	tgg	gga	ttt	acc	aca	cca	gat	aaa	aaa	cat	960
Arg	Gln	His	Leu	Leu	Arg	Trp	Gly	Phe	Thr	Thr	Pro	Asp	Lys	Lys	His	
	305				310					315					320	
cag	aaa	gaa	cct	cca	ttt	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
				325					330					335		
aaa	tgg	aca	gta	cag	cct	ata	gta	ctg	cca	gaa	aaa	gac	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr	
			340					345					350			

gtc  
Val

1059

<210> 42  
<211> 1053  
<212> DNA  
<213> Human Immunodeficiency Virus (HIV)

<220>  
<221> CDS  
<222> (0)...(297)  
<223> HIV Protease

<221> CDS  
<222> (298)...(1053)  
<223> Portion of HIV Reverse Transcriptase

<400> 42  
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata arg ata ggg 48  
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Xaa Ile Gly  
1 5 10 15  
ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta 96  
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
20 25 30  
tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atg ata ggg 144  
Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly  
35 40 45  
gga att gga ggt ttt atm aaa gta aga cag tat gat cag ata cyc ata 192  
Gly Ile Gly Gly Phe Xaa Lys Val Arg Gln Tyr Asp Gln Ile Xaa Ile  
50 55 60  
gaa atc tgt gga yat aaa gct ata ggt acr gta tta gta gga ccc acg 240  
Glu Ile Cys Gly Xaa Lys Ala Ile Gly Xaa Val Leu Val Gly Pro Thr  
65 70 75 80  
cct gtc aac rta att gga aga aat ctg wtg act cag att ggt tgc act 288  
Pro Val Asn Xaa Ile Gly Arg Asn Leu Xaa Thr Gln Ile Gly Cys Thr  
85 90 95  
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
100 105 110  
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
115 120 125  
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa gga 432  
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly  
130 135 140  
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt 480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
145 150 155 160  
gcc ata aag aaa aaa gac agt act aaa tgg aga aaa ttr gta gat ttc 528  
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Xaa Val Asp Phe  
165 170 175  
aga gaa ctt aat aag aaa act caa gac ttc tgg gaa gtc caa tta gga 576  
Arg Glu Leu Asn Lys Lys Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
180 185 190



ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aag Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	gta Val	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	kgg Xaa 240	720
att Ile	aga Arg	tay Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	tty Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	cta Leu	gtt Val	att Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	ara Xaa 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	gca Ala	gtg Val 340	caa Gln	cct Pro	ata Ile	gtg Val 345	ctg Leu	cca Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp		1053

```
<210> 43
<211> 1082
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

```
<220>
<221> CDS
<222> (0) ... (297)
<223> HIV Protease
```

```
<221> CDS
<222> (298)...(1082)
<223> Portion of HIV Reverse Transcriptase
```

<400> 43																
cct	caa	atc	act	ctt	tgg	caa	cga	ccc	ctt	gtc	aca	rta	aag	rta	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Xaa	Lys	Xaa	Gly	
1				5					10					15		
ggg	caa	cta	aag	gaa	gct	yta	ttr	gat	aca	gga	gca	gat	gat	aca	gta	96
Gly	Gln	Leu	Lys	Glu	Ala	Xaa	Xaa	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
tta	gaa	gaa	atg	aat	tta	cca	gga	aga	tgg	aaa	cca	aaa	atg	ata	ggg	144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	

			35			40						45						
gga Gly	att Ile	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp	cag Gln	ata Ile	ccc Pro	ata Ile		192	
			50				55				60							
gaa Glu	aty Xaa	tgt Cys	ggg Gly	cat His	aaa Lys	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val	tta Leu	gta Val	ggg Gly	cct Pro	aca Thr		240	
			65				70				75				80			
cct Pro	gtc Val	aac Asn	ata Ile	att Ile	gga Gly	aga Arg	aat Asn	ttg Leu	ttg Leu	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys	act Thr		288	
				85				90								95		
tta Leu	aat Asn	ttt Phe	cct Pro	att Ile	agt Ser	cct Pro	att Ile	gaa Glu	act Thr	gta Val	cca Pro	gta Val	aaa Lys	tta Leu	aag Lys		336	
			100				105								110			
cca Pro	gga Gly	atg Met	gat Asp	ggc Gly	ccc Pro	aaa Lys	gtt Val	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu	aca Thr	gaa Glu	gaa Glu		384	
			115				120				125							
aaa Lys	ata Ile	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met	gaa Glu	aaa Lys	gaa Glu	ggg Gly		432	
			130				135				140							
aaa Lys	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr	aat Asn	act Thr	cca Pro	gta Val	ttt Phe		480	
			145				150				155				160			
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp	ttc Phe		528	
				165				170				175						
aga Arg	gaa Glu	ctt Leu	aat Asn	aag Lys	aga Arg	act Thr	caa Gln	gac Asp	ttt Phe	tgg Trp	gaa Glu	gtt Val	caa Gln	tta Leu	gga Gly		576	
			180				185								190			
ata Ile	ccg Pro	cat His	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys	aag Lys	aaa Lys	aag Lys	tca Ser	gta Val	aca Thr	gta Val	ctg Leu		624	
			195				200				205							
gat Asp	gtg Val	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp	aaa Lys	gac Asp	ttc Phe	agg Arg		672	
			210				215				220							
aaa Lys	tat Tyr	ast Xaa	gca Ala	ttt Phe	acc Thr	ata Ile	ccg Pro	agt Ser	ata Ile	aac Asn	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly		720	
			225				230				235				240			
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr	aat Asn	gtg Val	ctt Leu	ccg Pro	cag Gln	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser	cca Pro		768	
				245				250				255						
gca Ala	ata Ile	ttc Phe	caa Gln	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys	atc Ile	tta Leu	gaa Glu	cct Pro	ttt Phe	aga Arg	aaa Lys		816	
			260				265				270							
caa Gln	aat Asn	cca Pro	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp	ttg Leu	tat Tyr	gta Val			

Arg 305	Gln	His	Leu	Leu	Lys 310	Trp	Xaa	Phe	Thr	Thr 315	Pro	Asp	Lys	Lys	His 320	
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
				325					330					335		
aaa	tgg	aca	gta	caa	ccg	ata	gag	ctg	cca	gaa	aaa	gaa	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Glu	Leu	Pro	Glu	Lys	Glu	Ser	Trp	Thr	
			340					345					350			
gtc	aat	gac	ata	cag	aag	tta	gtg	gg								1082
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val									
		355					360									
<210> 44																
<211> 1116																
<212> DNA																
<213> Human Immunodeficiency Virus (HIV)																
<220>																
<221> CDS																
<222> (0)...(297)																
<223> HIV Protease																
<221> CDS																
<222> (298)...(1116)																
<223> Portion of HIV Reverse Transcriptase																
<400> 44																
cct	cag	atc	act	ctt	tgg	caa	cga	ccc	atc	gtc	aca	gta	aag	ata	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Ile	Val	Thr	Val	Lys	Ile	Gly	
1				5					10					15		
ggg	caa	cta	aag	gaa	gct	yta	tta	gat	aca	gga	gca	gat	gat	aca	gta	96
Gly	Gln	Leu	Lys	Glu	Ala	Xaa	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
tta	gaa	gaa	atg	aat	tta	cca	gga	aaa	tgg	aaa	cca	aaa	ata	ata	ggg	144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Lys	Trp	Lys	Pro	Lys	Ile	Ile	Gly	
		35					40					45				
gga	att	gga	ggt	ttt	gcc	aaa	gta	aga	cag	tat	gat	cag	ata	ccc	ata	192
Gly	Ile	Gly	Gly	Phe	Ala	Lys	Val	Arg	Gln	Tyr	As					

aaa att tca aag att ggg cct gaa aat cca tac aat act cca gta ttt	480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe	
145 150 155 160	
gcc ata aag aaa aaa aac agy act wga tgg aga aaa tta gta gat ttc	528
Ala Ile Lys Lys Lys Asn Xaa Thr Xaa Trp Arg Lys Leu Val Asp Phe	
165 170 175	
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa ttr gga	576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Xaa Gly	
180 185 190	
ata cca cat ccc tca ggg tta aaa aag aam aaa tca gta aca gta ctg	624
Ile Pro His Pro Ser Gly Leu Lys Lys Xaa Lys Ser Val Thr Val Leu	
195 200 205	
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg	672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg	
210 215 220	
aaa tat act gca ttt acc ata cct agt rta aac aat gag aca cca ggg	720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Xaa Asn Asn Glu Thr Pro Gly	
225 230 235 240	
att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca	768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg aca aga atc cta gag cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Arg Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
cag aat cca gac ata gtt atc tat caa tac gtg gat gac ttg ctt gta	864
Gln Asn Pro Asp Ile Val Ile Tyr Gln Tyr Val Asp Asp Leu Leu Val	
275 280 285	
gga tct gat tta gaa ata ggg caa cat aga gca aaa ata gag gaa ctg	912
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Ala Lys Ile Glu Glu Leu	
290 295 300	
aga caa cat ctg ttg agg tgg ggg ttt atc aca cca gac gaa aaa cat	960
Arg Gln His Leu Leu Arg Trp Gly Phe Ile Thr Pro Asp Glu Lys His	
305 310 315 320	
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag ccc ata gtg ctg cca gaa aaa gay agc tgg act	1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gac ata caa aag tta gtg gga aaa ttg aat tgg gca agc cag	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tat gca ggg	1116
Ile Tyr Ala Gly	
370	

<210> 45  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)  
 <220>

<221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

```

<400> 45
cct cag atc act ctt tgg caa cga ccc rtc gtc aca ata aag ata ggg      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Ile Gly
  1                    5                    10                    15

ggg cag cta aag gaa gct cta tta gat aca gga gca gac gat aca gta      96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
                20                    25                    30

tta gaa gaa atg aat tta cca gga aaa tgg aaa cca aaa atg ata gtg      144
Leu Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Val
                35                    40                    45

gga att gga gga ttt gtc aaa gta aaa cag tat gag caa ata cct gta      192
Gly Ile Gly Gly Phe Val Lys Val Lys Gln Tyr Glu Gln Ile Pro Val
  50                    55                    60

gaa atc tgt gga cat aaa gct gta ggt aca gta tta gta gga cct aca      240
Glu Ile Cys Gly His Lys Ala Val Gly Thr Val Leu Val Gly Pro Thr
  65                    70                    75                    80

cct gcc aac ata att gga aga aat ctg ttg act cag att ggt tgc act      288
Pro Ala Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
                85                    90                    95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag      336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
                100                    105                    110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca aaa gar      384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Lys Glu
                115                    120                    125

aaa ata maa gca ttg gta gaa att tgt aca gaa atg gaa aag gaa gga      432
Lys Ile Xaa Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly
  130                    135                    140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gtg ttt      480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe
  145                    150                    155                    160

gct ata aag aaa aag aac agt gat aga tgg aga aaa tta gta gat ttc      528
Ala Ile Lys Lys Lys Asn Ser Asp Arg Trp Arg Lys Leu Val Asp Phe
                165                    170                    175

aga gaa ctt aat aag agg act caa gac ttc tgg gaa att caa tta gga      576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Ile Gln Leu Gly
                180                    185                    190

ata cca cat ccc gca ggg tta aaa aag aag aaa tca gta aca rta cta      624
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Xaa Leu
                195                    200                    205

gat gtg ggt gat gca tat ttt tca rtt ccc tta gat aaa gaa ttc agg      672
Asp Val Gly Asp Ala Tyr Phe Ser Xaa Pro Leu Asp Lys Glu Phe Arg
  210                    215                    220

aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg      720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly
  
```

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

225	230	235	240	
att aga tat	caa tac aat gtg ctt cca	caa gga tgg aaa gga tca cca		768
Ile Arg Tyr	Gln Tyr Asn Val Leu Pro	Gln Gly Trp Lys Gly Ser Pro		
	245	250	255	
gca ata ttc	caa gct agc atg aca aaa atc tta gag cct ttc aga aaa		816	
Ala Ile Phe	Gln Ala Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys			
	260	265	270	
caa aat cca	gaa cta gtt atc tat caa tac gtg gat gac ttg tat gta		864	
Gln Asn Pro	Glu Leu Val Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val			
	275	280	285	
gga tct gac	tta gaa ata gga cag cat aga aca aaa ata gag gaa ctg		912	
Gly Ser Asp	Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu			
	290	295	300	
aga gaa cat	ctg tta aaa tgg gga tta ttc aca cca gac cag aaa cat		960	
Arg Glu His	Leu Leu Lys Trp Gly Leu Phe Thr Pro Asp Gln Lys His			
	305	310	315	320
cag aaa gaa	ccc cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat		1008	
Gln Lys Glu	Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			
	325	330	335	
aaa tgg act	ata cag cct atg gtg ctg cca gaa aaa gac agc tgg act		1056	
Lys Trp Thr	Ile Gln Pro Met Val Leu Pro Glu Lys Asp Ser Trp Thr			
	340	345	350	
gtc aat gac	cta cag aag tta gtg gga aaa ttg aat tgg gca agt cag		1104	
Val Asn Asp	Leu Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln			
	355	360	365	
att tat cca	ggg		1116	
Ile Tyr Pro	Gly			
	370			
<210> 46				
<211> 1116				
<212> DNA				
<213> Human Immunodeficiency Virus (HIV)				
<220>				
<221> CDS				
<222> (0)...(297)				
<223> HIV Protease				
<221> CDS				
<222> (298)...(1116)				
<223> Portion of HIV Reverse Transcriptase				
<400> 46				
cct caa atc act	ctt tgg caa cga ccc ctc gtc aca ata aaa gta ggg		48	
Pro Gln Ile Thr	Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Val Gly			
1	5	10	15	
ggg caa cta aag	gaa gct cta tta gat aca gga gca gat gat aca gta		96	
Gly Gln Leu Lys	Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val			
	20	25	30	
tta gaa gaa atg	aat ttg cca gga agg tgg aaa cca aaa atg ata ggg		144	
Leu Glu Glu Met	Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly			
	35	40	45	
gga att gga ggt	ttt atc aaa gta aga cag tat gat cag ata tcc ata		192	

Gly	Ile	Gly	Gly	Phe	Ile	Lys	Val	Arg	Gln	Tyr	Asp	Gln	Ile	Ser	Ile	
	50					55					60					
gaa	atc	tgt	gga	cat	aaa	gct	ata	ggg	aca	gta	tta	gta	gga	cct	aca	240
Glu	Ile	Cys	Gly	His	Lys	Ala	Ile	Gly	Thr	Val	Leu	Val	Gly	Pro	Thr	
	65				70				75						80	
cct	gtc	aac	ata	att	gga	aga	aat	ctg	ttg	act	cag	att	ggg	tgc	act	288
Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Ile	Gly	Cys	Thr	
				85				90						95		
tta	aat	ttt	cct	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gac	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gag	att	tgt	aca	gaa	atg	gaa	aag	gaa	gga	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly	
	130					135					140					
aaa	att	tca	aaa	att	ggg	cct	gaa	aac	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aaa	gac	agt	act	aag	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asp	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aaa	aga	act	caa	gac	ttc	tgg	gag	gtt	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	cta	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu	
		195				200						205				
gat	gtg	ggc	gat	gca	tat	ttc	tca	gtt	ccc	tta	gat	gaa	gac	ttc	aga	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Glu	Asp	Phe	Arg	
	210				215						220					
aaa	tat	act	gca	ttt	acc	ata	cct	agt	ata	aac	aat	gag	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
act	aga	tat	cag	tac	aat	gtg	ctc	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Thr	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
				245					250					255		
gca	ata	ttc	caa	tgt	agc	atg	aca	aaa	atc	tta	gag	cct	ttt	aga	aaa	816
Ala	Ile	Phe	Gln	Cys	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			
caa	aat	cca	gac	cta	gtt	atc	tat	caa	tac	atg	gat	gat	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Leu	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
		275					280					285				
gga	tct	gac	tta	gaa	ata	gga	cag	cat	aga	aca	aaa	ata	gag	gaa	ctg	912
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu	
	290					295					300					
aga	caa	cat	ctg	ttg	agg	tgg	gga	ttt	acc	acc	cca	gac	aaa	aaa	cat	960
Arg	Gln	His	Leu	Leu	Arg	Trp	Gly	Phe	Thr	Thr	Pro	Asp	Lys	Lys	His	
	305				310					315					320	

cag aaa gaa cct cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gtr cag cct ata gtg ctg cca gaa aaa gac agc tgg act	1056
Lys Trp Thr Xaa Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tac cca ggg	1116
Ile Tyr Pro Gly	
370	
<210> 47	
<211> 1116	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1116)	
<223> Portion of HIV Reverse Transcriptase	
<400> 47	
cct caa atc act ctt tgg caa cga ccc ctc gtc aca gta aag ata ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Val Lys Ile Gly	
1 5 10 15	
ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
tta gaa gac atg tgt ttg cca gga aga tgg aaa cca aaa atg ata ggg	144
Leu Glu Asp Met Cys Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly	
35 40 45	
gga att gga ggt ttt atc aaa gta aga caa tat gat cag gta gcc atg	192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Ala Met	
50 55 60	
gaa atc tgt gga cat aag gct ata ggt aca gta tta ata gga cct aca	240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr	
65 70 75 80	
cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act	288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr	
85 90 95	
tta aat ttt ccc att agc cct att gaa act gta ccm gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Xaa Val Lys Leu Lys	
100 105 110	
cca ggr atg gat ggt cca agg gtt aaa caa tgg cca ttg aca gaa gaa	384
Pro Xaa Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata ara gca tta gta gaa att tgt aca gaa atg gaa aag gaa gga	432
Lys Ile Xaa Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly	
130 135 140	



[illegible]

```
<210> 48
<211> 1115
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

Figure 1 displays 16 micrographs arranged vertically, showing the life cycle of the nematode *C. elegans*. The stages are labeled on the left:

- 1. Egg
- 2. 1st larval stage
- 3. 2nd larval stage
- 4. 3rd larval stage
- 5. 4th larval stage
- 6. Adult
- 7. Egg
- 8. 1st larval stage
- 9. 2nd larval stage
- 10. 3rd larval stage
- 11. 4th larval stage
- 12. Adult
- 13. Egg
- 14. 1st larval stage
- 15. 2nd larval stage
- 16. 3rd larval stage

The images illustrate the morphological changes from a small egg to a fully developed adult worm, including the development of head, tail, and internal structures.

Figure 1 displays 16 micrographs showing various stages of the life cycle of the nematode *C. elegans*. The stages are labeled on the left: 1. Egg, 2. 1st larval stage, 3. 2nd larval stage, 4. 3rd larval stage, 5. 4th larval stage, 6. Adult, 7. Egg, 8. 1st larval stage, 9. 2nd larval stage, 10. 3rd larval stage, 11. 4th larval stage, 12. Adult, 13. Egg, 14. 1st larval stage, 15. 2nd larval stage, 16. 3rd larval stage. The images show the morphological changes from a small egg to a fully developed adult worm, including larval stages with distinct head, tail, and body segments.

Figure 1 consists of 15 subplots, each showing the effect of a different chemical treatment on the growth of *E. coli* O157:H7. The y-axis for all plots is 'log<sub>10</sub> CFU/g' ranging from 0 to 8. The x-axis represents time in minutes, ranging from 0 to 120. The subplots are labeled (a) through (m). Each plot shows a line graph of bacterial concentration over time. The treatments include Control, NaCl, NaOCl, Na<sub>2</sub>O<sub>2</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>7</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, and Na<sub>2</sub>S<sub>2</sub>O<sub>7</sub>. The Control plot shows a steady increase in bacterial concentration over time. The other plots show varying degrees of inhibition or reduction in bacterial growth, with some treatments showing a significant decrease in concentration over time.

Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly	
225					230					235					240	
att	aga	tat	cag	tac	aat	gtg	ctk	cca	cag	gga	tgg	aag	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Xaa	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
			245						250					255		
gca	ata	ttc	caa	agt	agc	atg	aca	aaa	atc	ttg	gag	ccc	ttt	aga	aaa	816
Ala	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			
caa	aat	cca	gac	cta	gtt	atc	tat	caa	tac	atg	gat	gat	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Leu	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
		275					280					285				
ggc	tct	gac	tta	gaa	ata	ggg	cag	cat	aga	aca	aaa	ata	gag	gaa	ctg	912
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu	
	290					295					300					
aga	caa	cat	ctg	ttg	aag	tgg	gga	ttt	acc	aca	cca	gat	aaa	aaa	cat	960
Arg	Gln	His	Leu	Leu	Lys	Trp	Gly	Phe	Thr	Thr	Pro	Asp	Lys	Lys	His	
305					310					315					320	
cag	aaa	gaa	cct	cca	ttt	ctt	tgg	atg	ggt	tat	gaa	ctc	cat	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
			325						330					335		
aaa	tgg	aca	gta	cag	cct	ata	gtg	ctg	cca	gaa	aaa	gac	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr	
			340					345					350			
gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	ttg	aat	tgg	gca	agt	cag	1104
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Ser	Gln	
		355					360					365				
att	tcc	car	ga													1115
Ile	Ser	Gln														
	370															
<210>	49															
<211>	1116															
<212>	DNA															
<213>	Human Immunodeficiency Virus (HIV)															
<220>																
<221>	CDS															
<222>	(0)...(297)															
<223>	HIV Protease															
<221>	CDS															
<222>	(298)...(1116)															
<223>	Portion of HIV Reverse Transcriptase															
<400>	49															
cct	cag	atc	act	ctt	tgg	caa	cga	ccc	ctc	gtc	rca	ata	aag	ata	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Xaa	Ile	Lys	Ile	Gly	
1				5					10					15		
ggg	cag	cta	aag	gaa	gct	cta	tta	gat	aca	gga	gca	gat	gat	aca	gta	96
Gly	Gln	Leu	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
tta	gaa	gaa	atg	aat	ttg	cca	gga	aga	tgg	aaa	cca	aag	atg	ata	ggg	144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	
		35					40					45				

gga Gly	att Ile 50	gga Gly	ggt Gly	ttc Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ccc Pro	ata Ile	192
gaa Glu 65	atc Ile	tgt Cys	ggc Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggc Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	cta Leu	ttg Leu 90	act Thr	cag Gln	att Ile	ggc Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aag Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	atc Ile	tgt Cys	aca Thr	gaa Glu 140	atg Met	gaa Glu	aag Lys	gaa Glu	ggg Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aam Xaa	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggc Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gaa Glu	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	acc Thr	gca Ala	ttt Phe	cca Pro 230	tcc Ser	cta Leu	gtt Val	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	gga Gly 240	720
atc Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttt Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp 285	gat Asp	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	gta Val	gag Glu	gag Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960

cag aaa gag cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat 1008  
 Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp  
 325 330 335

aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act 1056  
 Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr  
 340 345 350

gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agc cag 1104  
 Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
 355 360 365

att tac cca ggg 1116  
 Ile Tyr Pro Gly  
 370

<210> 50  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400> 50  
 cct cag atc act ctt tgg caa cga ccc ttc gtc aac ata aag ata ggg 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Pro Phe Val Asn Ile Lys Ile Gly  
 1 5 10 15

gga caa ctg aag gaa gct cta ttg gat aca gga gca gat gat aca gta 96  
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
 20 25 30

tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa ttg ata ggg 144  
 Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Leu Ile Gly  
 35 40 45

gga att gga ggt ttg gtc aaa gta aga cag tat gat cag ata cct gta 192  
 Gly Ile Gly Gly Xaa Val Lys Val Arg Gln Tyr Asp Gln Ile Pro Val  
 50 55 60

gaa att tgt gga cat aaa gyt ata ggt aca gtc tta gta gga cct aca 240  
 Glu Ile Cys Gly His Lys Xaa Ile Gly Thr Val Leu Val Gly Pro Thr  
 65 70 75 80

cct gcc aac ata att gga aga aat ctg ttg act cag att ggc tgc act 288  
 Pro Ala Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr  
 85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
 100 105 110

cca gga atg gat ggc ccg aga gtt aaa caa tgg cca ttg aca gaa gaa 384  
 Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu  
 115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gaa aag gaa gga 432  
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly

130				135				140								
aaa Lys 145	att Ile	tca Ser	aag Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	ata Ile	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	aac Asn	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	mam Xaa 200	aag Lys	aac Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gtg Val	cta Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	tat Tyr 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe 230	acc Thr	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tay Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	cag Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aga Arg 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtc Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gca Ala	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gag Glu 295	aaa Lys	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	agg Arg 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aag Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aaa Lys	gac Asp 350	agc Ser	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aaa Lys	tta Leu	gtg Val 360	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
att Ile	tat Tyr 370	gga Gly	ggg Gly													1116

- 81 -



[illegible]

```
<210> 52
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

- 83 -





[illegible]

```
<210> 53
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

[illegible]

130	135	140	
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt			480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe			
145	150	155	160
gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc			528
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe			
	165	170	175
aga gaa ctt aat aag aaa act caa gac ttc tgg gaa gtt caa tta gga			576
Arg Glu Leu Asn Lys Lys Thr Gln Asp Phe Trp Glu Val Gln Leu Gly			
	180	185	190
atc cca cat cct gca ggg tta aaa aag aaa aaa tca gta aca gta ctg			624
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu			
	195	200	205
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc cgg			672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg			
	210	215	220
aag tat act gca ttt acc ata cct agt aca aac aat gag aca cca gga			720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Thr Asn Asn Glu Thr Pro Gly			
	225	230	240
att aga tat cag tac aat gtg ctt cca caa gga tgg aaa gga tca cca			768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro			
	245	250	255
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt agg aat			816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Asn			
	260	265	270
aaa aat cca gac ata gtt atc tat caa tac gtg gat gat ttg tat gta			864
Lys Asn Pro Asp Ile Val Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val			
	275	280	285
gga tct gac cta gaa ata ggg cag cat aga gca aaa ata gag gaa ctg			912
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Ala Lys Ile Glu Glu Leu			
	290	295	300
aga gaa cat ctg ttg aag tgg ggg ttt act aca cca gac aaa aaa cat			960
Arg Glu His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His			
	305	310	315
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat			1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			
	325	330	335
aaa tgg aca gtc cag cct ata gag ctg cca gaa aaa gac agc tgg act			1056
Lys Trp Thr Val Gln Pro Ile Glu Leu Pro Glu Lys Asp Ser Trp Thr			
	340	345	350
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag			1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln			
	355	360	365
att tat gca gga			1116
Ile Tyr Ala Gly			
	370		

<210> 54  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)



[illegible]

```
<210> 55
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

- 88 -

gga att gga ggt ttt atc aaa gta aag cag tat gat cag gta ctt gta Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Asp Gln Val Leu Val 50 55 60	192
gaa att tgt gga cat ara gct ata ggt aca gta tta gta gga cct aca Glu Ile Cys Gly His Xaa Ala Ile Gly Thr Val Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgt act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca ggt atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta ata gaa att tgt aca gaa atg gaa aag gaa ggg Lys Ile Lys Ala Leu Ile Glu Ile Cys Thr Glu Met Glu Lys Glu Gly 130 135 140	432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480
gcc ata aag aaa aaa gac agt acc aaa tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 170 175	528
aga gaa ctt aat aag aaa acg caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Lys Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 180 185 190	576
ata cca cat ccc gca ggg tta aaa aag aaa aaa tca gta aca gta ctg Ile Pro His Pro Ala Gly Leu Lys Lys Lys Ser Val Thr Val Leu 195 200 205	624
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aag gac ttc agg Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg 210 215 220	672
aag tat act gca ttt acc ata cct agt gta aac aat gag aca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Val Asn Asn Glu Thr Pro Gly 225 230 235 240	720
att aga tat cag tac aat gtg ctg cca cag gga tgg aaa gga tca cca Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttt caa agt agc atg aca aaa atc tta gag cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys 260 265 270	816
caa aat cca gac atg gtt atc tat caa tac atg gat gat ttg tat gta Gln Asn Pro Asp Met Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val 275 280 285	864
gga tct gac tta gaa ata gag cag cat aga rca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Glu Gln His Arg Xaa Lys Ile Glu Glu Leu 290 295 300	912
agg cag cat ctg ttg agg tgg gga ttt acc aca cca gac aaa aag cat Arg Gln His Leu Leu Arg Trp Gly Phe Thr Thr Pro Asp Lys Lys His 305 310 315 320	960

cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag cct ata ktg ctg cca gaa aaa gac agc tgg act	1056
Lys Trp Thr Val Gln Pro Ile Xaa Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tam ccc ngg	1116
Ile Xaa Pro Xaa	
370	
<210> 56	
<211> 1116	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1116)	
<223> Portion of HIV Reverse Transcriptase	
<400> 56	
cct caa atc act ctt tgg caa cga ccc att gtc aca ata aag ata ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly	
1 5 10 15	
ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
tta gaa gaa atg aat ttg cca gga aaa tgg aaa cca aaa atg ata ggg	144
Leu Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly	
35 40 45	
gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata acc ata	192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Thr Ile	
50 55 60	
gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca	240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr	
65 70 75 80	
cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act	288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr	
85 90 95	
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aaa gaa ggg	432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly	

130	135	140	
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt			480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe			
145	150	155	160
gcc ata aag aaa aaa gat agt act aaa tgg aga aaa tta gta gat ttc			528
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe			
	165	170	175
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gta caa tta gga			576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly			
	180	185	190
ata cca cat ccc gca ggg tta aaa aag aaa aaa tca gta aca gta cta			624
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu			
	195	200	205
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gaa ttc agg			672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Glu Phe Arg			
	210	215	220
aag tat act gca ttc acc ata cct agt ata aac aat gag aca cca ggg			720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly			
	225	230	235
att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca			768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro			
	245	250	255
gca ata ttc caa agc agc atg aca aaa att tta gaa cct ttt aga aaa			816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys			
	260	265	270
caa aat cca gaa ata gtt atc tat caa tac atg gat gat ttg tat gta			864
Gln Asn Pro Glu Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val			
	275	280	285
gga tct gac tta raa ata gag cag cat aga aca aaa ata gag gaa ctg			912
Gly Ser Asp Leu Xaa Ile Glu Gln His Arg Thr Lys Ile Glu Glu Leu			
	290	295	300
aga caa cat ctg ttg agg tgg gga ttt acc aca cca gac aaa aag cat			960
Arg Gln His Leu Leu Arg Trp Gly Phe Thr Thr Pro Asp Lys Lys His			
	305	310	315
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctg cat cct gat			1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			
	325	330	335
aaa tgg aca gta cag cct ata gtg ctg cca gaa cag gac agc tgg act			1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Gln Asp Ser Trp Thr			
	340	345	350
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag			1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln			
	355	360	365
att tat cca ggg			1116
Ile Tyr Pro Gly			
	370		

<210> 57

<211> 1116

<212> DNA

<213> Human Immunodeficiency Virus (HIV)



<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400> 57

cct cag atc act ctt tgg caa cga ccc ctc gtc aca gta aag tta ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Val Lys Leu Gly	
1 5 10 15	
ggg caa cta atg gaa gtt cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Met Glu Val Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
rta gaa gaa ata agt tta cca gga aga tgg aaa cca aaa atg ata ggg	144
Xaa Glu Glu Ile Ser Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly	
35 40 45	
gga att gga ggt ttt gtc aaa gta aaa cag tat gat cag gta ccc tta	192
Gly Ile Gly Gly Phe Val Lys Val Lys Gln Tyr Asp Gln Val Pro Leu	
50 55 60	
gaa att tgt gga aaa aag gct ata ggt aca gta tta gta gga cct aca	240
Glu Ile Cys Gly Lys Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr	
65 70 75 80	
cct gcc aac ata att gga aga aat ttt ttg gct cag att ggt tgc act	288
Pro Ala Asn Ile Ile Gly Arg Asn Phe Leu Ala Gln Ile Gly Cys Thr	
85 90 95	
tta aat ttc ccc att agt cct att gaa act gta cca gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg	432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly	
130 135 140	
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt	480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe	
145 150 155 160	
gcc ata aag aaa aag aac agt act aga tgg aga aaa tta gta gat ttt	528
Ala Ile Lys Lys Lys Asn Ser Thr Arg Trp Arg Lys Leu Val Asp Phe	
165 170 175	
aga gaa ctt aat aag agg acs caa gac ttc tgg gaa gtt caa tta gga	576
Arg Glu Leu Asn Lys Arg Xaa Gln Asp Phe Trp Glu Val Gln Leu Gly	
180 185 190	
ata cca cat ccc gca ggg tta aar aag aac aaa tca gta aca gta ctg	624
Ile Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu	
195 200 205	
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat cca gac ttc agg	672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Pro Asp Phe Arg	
210 215 220	
aag tat act gca ttt acc ata cct agt aca aac aat gag aca cca ggg	720





```

cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cca gat      1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp
325 330 335

aaa tgg aca gta cag cct ata aag ctg cca gac aaa gac agc tgg act      1056
Lys Trp Thr Val Gln Pro Ile Lys Leu Pro Asp Lys Asp Ser Trp Thr
340 345 350

gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag      1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln
355 360 365

att tat gca gga
Ile Tyr Ala Gly
370
1116

<210> 59
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase

<400> 59
cct caa atc act ctt tgg caa cga ccc tta gtc aca ata aag ata grg      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Xaa
1 5 10 15

ggg caa cta aaa gaa gct cta tta gat aca gga gca gat gat aca gta      96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val
20 25 30

tta gaa gaa ata aat ttg cca ggg aaa tgg aaa cca maa atg ata ggg      144
Leu Glu Glu Ile Asn Leu Pro Gly Lys Trp Lys Pro Xaa Met Ile Gly
35 40 45

gga att gga ggt ttt att aaa gta aga cag tat gat caa ata gcc ata      192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Ala Ile
50 55 60

gaa att tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca      240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr
65 70 75 80

cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act      288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr
85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag      336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys
100 105 110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa      384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu
115 120 125

aaa ata aaa gca tta rta gaa atc tgt aca gaa atg gaa aag gaa ggg      432
Lys Ile Lys Ala Leu Xaa Glu Ile Cys Thr Glu Met Glu Lys Glu Gly

```

130	135	140	
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt			480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe			
145	150	155	160
gcm ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc			528
Xaa Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe			
	165	170	175
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtc caa tta gga			576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly			
	180	185	190
ata cca cat ccc gca ggg tta aaa aag aaa aaa tca gta aca gta cta			624
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu			
	195	200	205
gat gtg ggt gat gca tat ttc tca gtt ccc tta gac caa gac ttc agg			672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Gln Asp Phe Arg			
	210	215	220
aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg			720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly			
	225	230	235
att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca			768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro			
	245	250	255
gca ata ttc caa agt agc atg aca agg atc tta gar cct ttt aga aaa			816
Ala Ile Phe Gln Ser Ser Met Thr Arg Ile Leu Glu Pro Phe Arg Lys			
	260	265	270
caa aat cca gaa ata gtc aty tat cag tac atg gat gat tta tat gta			864
Gln Asn Pro Glu Ile Val Xaa Tyr Gln Tyr Met Asp Asp Leu Tyr Val			
	275	280	285
gga tct gac tta gaa ata ggg cag cat aga aca aaa gta gag gaa ctg			912
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Val Glu Glu Leu			
	290	295	300
aga caa cat ctg ttg agr tgg ggg ttt tmc acg cca gac aaa aag cat			960
Arg Gln His Leu Leu Xaa Trp Gly Phe Xaa Thr Pro Asp Lys Lys His			
	305	310	315
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat			1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			
	325	330	335
aaa tgg aca gta cag act ata gaa ctg cca gaa aaa gat agc tgg act			1056
Lys Trp Thr Val Gln Thr Ile Glu Leu Pro Glu Lys Asp Ser Trp Thr			
	340	345	350
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag			1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln			
	355	360	365
ata tac cca ggg			1116
Ile Tyr Pro Gly			
370			

<210> 60

<211> 1116

<212> DNA

<213> Human Immunodeficiency Virus (HIV)















097069005.11000

Lys Tyr Thr Ala Phe Thr Ile Pro Ser Thr Asn Asn Glu Thr Pro Gly	
225 230 235 240	
att aga tat cag tac aat gtg ctt cca caa gga tgg aaa gga tca ccg	768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg acc aaa atc tta gaa cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
caa aat cca gaa atg gtt atc tat caa tac gtg gat gat ttg tat gta	864
Gln Asn Pro Glu Met Val Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val	
275 280 285	
gga tct gac tta gaa ata ggg cag cat aga ata aaa ata gag gaa tta	912
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Ile Lys Ile Glu Glu Leu	
290 295 300	
agg gaa cac cta ttg aag tgg gga ttt ttc acc cca gac gaa aag cat	960
Arg Glu His Leu Leu Lys Trp Gly Phe Phe Thr Pro Asp Glu Lys His	
305 310 315 320	
cag aaa gaa cct cca ttt ctt tgg atg ggt tat gaa ctt cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gtg cag cct ata aaa ctg cca gaa aaa gaa agc tgg act	1056
Lys Trp Thr Val Gln Pro Ile Lys Leu Pro Glu Lys Glu Ser Trp Thr	
340 345 350	
gtc aat gat ata cag aag tta gtg gga aaa tta aat tgg gca agc cag	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tat cca gga	1116
Ile Tyr Pro Gly	
370	
<210> 64	
<211> 1116	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1116)	
<223> Portion of HIV Reverse Transcriptase	
<400> 64	
cct cag atc act ctt tgg caa cga ccc atc gtc aca ata aag ata ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly	
1 5 10 15	
ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
tta gaa gaa atg aat tta cca gga aaa tgg aaa cca aaa atr ata ggg	144
Leu Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Xaa Ile Gly	
35 40 45	















cag aaa gaa cct cca ytc ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Xaa Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act	1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tat cca ggg att	1119
Ile Tyr Pro Gly Ile	
370	
<210> 68	
<211> 1119	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1119)	
<223> Portion of HIV Reverse Transcriptase	
<400> 68	
cct caa atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly	
1 5 10 15	
gga caa cta aaa gaa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
tta gaa gaa atg aat ttg cca ggg aaa tgg aaa cca aaa atg ata ggg	144
Leu Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly	
35 40 45	
gga atc gga gga ttt atc aaa gta aga cag tat gag cag ata cac ata	192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Glu Gln Ile His Ile	
50 55 60	
gaa atc tgt ggg cat aaa gct ata ggt aca gtr tta ata gga ccc aca	240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Xaa Leu Ile Gly Pro Thr	
65 70 75 80	
cct gtc aac ata att gga aga aat ctg ttg act cag att ggc tgc act	288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr	
85 90 95	
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gag	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa gga	432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly	



<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1119)  
 <223> Portion of HIV Reverse Transcriptase

<400> 69  
 cct cag atc act ctt tgg caa cga ccc cty gtc aca ata aag ata ggg 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Ile Gly  
 1 5 10 15

ggg caa yta aag gaa gct mta tta gay aca gga gca gat gat aca gtg 96  
 Gly Gln Xaa Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val  
 20 25 30

tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa ata ata ggg 144  
 Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly  
 35 40 45

gga att gga ggt ttt atc aaa gta aga gag tat gag cag ata caa gta 192  
 Gly Ile Gly Gly Phe Ile Lys Val Arg Glu Tyr Glu Gln Ile Gln Val  
 50 55 60

gaa atc tgt gga cat aag gct ata rgt aca gta tta ata gga cct aca 240  
 Glu Ile Cys Gly His Lys Ala Ile Xaa Thr Val Leu Ile Gly Pro Thr  
 65 70 75 80

cct gtc aac ata att gga aga aat cta atg act cag att ggt tgc act 288  
 Pro Val Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Thr  
 85 90 95

tta aat ttt ccc att agt cct att gag act gta ccg gta aaa tta aag 336  
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
 100 105 110

cca gga atg gat ggt cca aga gtt aaa caa tgg cca ttg aca gaa gaa 384  
 Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu  
 115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gaa aag gaa gga 432  
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly  
 130 135 140

aaa att tca aaa att ggg cct gaa aat cca tac aat acy ccr gta ttt 480  
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Xaa Xaa Val Phe  
 145 150 155 160

gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc 528  
 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
 165 170 175

aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga 576  
 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
 180 185 190

ata ccg cat ccc gca ggg tta aag aag aaa aaa tca gta aca gta ctr 624  
 Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Xaa  
 195 200 205

gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg 672  
 Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg  
 210 215 220

aag tac act gca ttt acc ata cct agt ata aac aat gag aca cca gga 720

Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly	
225					230					235					240	
att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
				245					250					255		
gca	ata	ttc	caa	agt	agc	atg	aca	aaa	atc	tta	gaa	cct	ttt	aga	aaa	816
Ala	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			
caa	aat	cca	gac	ata	gtt	atc	tat	car	tac	atg	gat	gac	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
		275					280					285				
gga	tct	gac	tta	gaa	ata	ggg	cag	cat	aga	aca	aaa	ata	gag	gaa	cta	912
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu	
	290					295					300					
aga	caa	cat	ctg	tkg	agg	tgg	gga	ttt	tac	aca	cca	gac	aaa	aaa	cat	960
Arg	Gln	His	Leu	Xaa	Arg	Trp	Gly	Phe	Tyr	Thr	Pro	Asp	Lys	Lys	His	
	305				310					315					320	
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cac	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
			325						330					335		
aaa	tgg	aca	gta	cag	cct	ata	gtg	ctr	cca	gaa	aaa	gac	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Xaa	Pro	Glu	Lys	Asp	Ser	Trp	Thr	
			340				345						350			
gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	tta	aat	tgg	gag	agt	cag	1104
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Ser	Gln	
		355					360					365				
att	tat	tca	ggg	att												1119
Ile	Tyr	Ser	Gly	Ile												
		370														
<210> 70																
<211> 1119																
<212> DNA																
<213> Human Immunodeficiency Virus (HIV)																
<220>																
<221> CDS																
<222> (0)...(297)																
<223> HIV Protease																
<221> CDS																
<222> (298)...(1119)																
<223> Portion of HIV Reverse Transcriptase																
<400> 70																
cct	caa	atc	act	ctt	tgg	caa	cga	ccc	cty	gtc	kca	ata	aag	gta	ggr	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Xaa	Val	Xaa	Ile	Lys	Val	Xaa	
	1			5					10					15		
ggg	caa	mta	aag	gaa	gct	yta	tta	gat	aca	gga	gca	gat	gat	aca	gta	96
Gly	Gln	Xaa	Lys	Glu	Ala	Xaa	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
tta	gaa	gaa	atg	aat	ttg	cca	gga	aga	tgg	aaa	cca	aaa	atg	ata	ggg	144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	
		35					40					45				



cag	aaa	gaa	ccc	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
				325					330					335		
aaa	tgg	aca	gta	car	ccc	ata	gtg	ttg	cca	gaa	aaa	gac	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr	
			340					345					350			
gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	ttg	aat	tgg	gca	agt	cag	1104
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Ser	Gln	
		355					360					365				
att	tay	gsa	ggg	att												1119
Ile	Tyr	Xaa	Gly	Ile												
			370													

<210> 71  
 <211> 1119  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease  
  
 <221> CDS  
 <222> (298)...(1119)  
 <223> Portion of HIV Reverse Transcriptase

<400> 71																
cct	caa	atc	act	ctt	tgg	caa	cga	ccc	atc	gtc	tca	ata	aag	ata	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Ile	Val	Ser	Ile	Lys	Ile	Gly	
1				5					10					15		
ggg	gca	aat	aaa	gaa	gct	cta	tta	gat	aca	gga	gca	gat	gat	aca	gta	96
Gly	Ala	Asn	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
tta	gaa	gaa	atg	aat	ttg	cca	gga	aga	tgg	aag	cca	aaa	atg	ata	gtg	144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Val	
			35				40					45				
gga	att	gga	ggg	ttt	agc	aaa	gta	aga	caa	tat	gat	cag	ata	ccc	ata	192
Gly	Ile	Gly	Gly	Phe	Ser	Lys	Val	Arg	Gln	Tyr	Asp	Gln	Ile	Pro	Ile	
	50					55					60					
gaa	atc	tgc	gga	cgt	aaa	gtt	gta	ggg	tca	gta	tta	ata	gga	cct	aca	240
Glu	Ile	Cys	Gly	Arg	Lys	Val	Val	Gly	Ser	Val	Leu	Ile	Gly	Pro	Thr	
	65				70					75					80	
cct	gcc	aac	ata	att	gga	aga	aat	ctg	ttg	act	cag	ctt	ggc	tgt	act	288
Pro	Ala	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Leu	Gly	Cys	Thr	
				85					90					95		
tta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	aaa	gag	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Lys	Glu	
			115				120					125				
aaa	ata	aaa	gca	tta	ata	gaa	att	tgt	aca	gaa	ttg	gaa	gaa	gma	gga	432
Lys	Ile	Lys	Ala	Leu	Ile	Glu	Ile	Cys	Thr	Glu	Leu	Glu	Glu	Xaa	Gly	



[illegible]

```
<210> 72
<211> 1119
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1119)  
 <223> Portion of HIV Reverse Transcriptase

<400> 72

cct	cag	atc	act	ctt	tgg	caa	cga	ccc	cty	gtc	aca	ata	aag	atc	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Xaa	Val	Thr	Ile	Lys	Ile	Gly	
1				5					10					15		
ggg	caa	tta	aag	gaa	gct	cta	tta	gat	aca	gga	gca	gat	gat	aca	gta	96
Gly	Gln	Leu	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
ata	gaa	gaa	atg	aat	ttg	cca	gga	aga	tgg	aaa	cca	aaa	atg	ata	ggg	144
Ile	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	
			35				40					45				
gga	att	gga	ggt	ttt	rtc	aaa	gta	aga	caa	tat	gat	cag	gta	ccc	ata	192
Gly	Ile	Gly	Gly	Phe	Xaa	Lys	Val	Arg	Gln	Tyr	Asp	Gln	Val	Pro	Ile	
	50					55					60					
gaa	att	tgc	gga	cat	aaa	gct	ata	ggt	aca	gta	tta	ata	gga	cct	aca	240
Glu	Ile	Cys	Gly	His	Lys	Ala	Ile	Gly	Thr	Val	Leu	Ile	Gly	Pro	Thr	
65					70				75						80	
cct	gyc	aac	ata	att	gga	aga	aac	ctg	ttg	act	caa	ctt	ggc	tgc	act	288
Pro	Xaa	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Leu	Gly	Cys	Thr	
				85				90					95			
tta	aat	ttt	cca	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gaa	att	tgt	aca	gaa	ctg	gaa	aaa	gga	agg	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Leu	Glu	Lys	Gly	Arg	
	130					135					140					
aaa	aat	tac	aaa	att	ggg	cct	gaa	aac	cca	tac	aat	act	cca	gta	ttt	480
Lys	Asn	Tyr	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
145					150					155					160	
gcc	ata	aag	aaa	aaa	gac	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asp	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aag	aga	act	caa	gac	ttc	tgg	gaa	gtt	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	cct	gca	ggg	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu	
			195				200					205				
gat	gtg	ggt	gat	gca	tat	ttc	tca	gtt	ccc	tta	gat	aag	gac	ttc	agg	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Lys	Asp	Phe	Arg	
	210					215					220					
aag	tat	act	gca	ttt	acc	ata	cct	agc	ata	aac	aat	gag	aca	cca	ggg	720

Lys 225	Tyr	Thr	Ala	Phe	Thr 230	Ile	Pro	Ser	Ile	Asn 235	Glu	Thr	Pro	Gly 240		
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctc Leu	cca Pro	cag Gln 250	gga Trp	tgg Lys	aaa Gly	gga Ser 255	tca Pro	cca Pro	768
gcm Xaa	ata Ile	ttc Phe	caa Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gaa Glu	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp 285	gat Asp	ttg Leu	tat Tyr	gta Val	864
ggg Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	cga Arg	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly 330	tat Tyr	gag Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr 340	gta Val	caa Gln	cct Pro	ata Ile	gtg Val 345	cta Leu	cca Pro	gag Glu	aaa Lys	gac Asp 350	agc Ser	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp 355	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val 360	gga Gly	aag Lys	tta Leu	aat Asn	tgg Trp 365	gca Ala	agt Ser	cag Gln	1104
ata Ile	tac Tyr 370	gca Ala	ggg Gly	att Ile												1119
<p>&lt;210&gt; 73</p> <p>&lt;211&gt; 1119</p> <p>&lt;212&gt; DNA</p> <p>&lt;213&gt; Human Immunodeficiency Virus (HIV)</p> <p>&lt;220&gt;</p> <p>&lt;221&gt; CDS</p> <p>&lt;222&gt; (0)...(297)</p> <p>&lt;223&gt; HIV Protease</p> <p>&lt;221&gt; CDS</p> <p>&lt;222&gt; (298)...(1119)</p> <p>&lt;223&gt; Portion of HIV Reverse Transcriptase</p> <p>&lt;400&gt; 73</p>																
cct Pro 1	caa Gln	atc Ile	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ttc Phe 10	gtc Val	aca Thr	gta Val	aag Lys 15	ata Ile	ggg Gly	48
ggg Gly	cag Gln	cta Leu	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp 30	aat Asn	aca Thr	gta Val	96
tta Leu	gaa Glu 35	gaa Met	atg Met	aat Asn	tta Leu	ccg Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys 45	cca Pro	aaa Lys 45	atg Met	ata Ile	ggg Gly	144

gga att gga ggt ttt atc aaa gta aga cag tat gat cag rta ccc ata	192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Xaa Pro Ile	
50 55 60	
gaa atc tgt gga cac aaa gct ata ggt aca gta tta ata gga cct aca	240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr	
65 70 75 80	
cct gtc aac ata att gga aga gat ctg ttg act cag ctt ggt tgc act	288
Pro Val Asn Ile Ile Gly Arg Asp Leu Thr Gln Leu Gly Cys Thr	
85 90 95	
tta aat ttt ccc att agt cct att gat act gta cca gta aaa tta aaa	336
Leu Asn Phe Pro Ile Ser Pro Ile Asp Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta gta gaa att tgt aca gaa ctg gaa aag gaa ggg	432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly	
130 135 140	
aag att tca aaa att ggg cct gaa aat cca tac aat acc cca gta ttt	480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe	
145 150 155 160	
gct ata aag aaa aaa gac agt act aaa tgg aga aag tta gta gat ttc	528
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe	
165 170 175	
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga	576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly	
180 185 190	
ata cca cat ccc gcg ggg tta aaa aag aac aaa tca gta aca gta ctg	624
Ile Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu	
195 200 205	
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg	672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg	
210 215 220	
aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg	720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly	
225 230 235 240	
att aga tat cag tac aat gtg ctt ccc cag gga tgg aaa gga tca cca	768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg aca aaa att tta gag cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
cag aat cca gac ata gtt atc tac caa tac gtg gat gac ttg tat gta	864
Gln Asn Pro Asp Ile Val Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val	
275 280 285	
gga tct gac tta gaa ata ggg cag cat aga gca aaa ata gat gag ctg	912
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Ala Lys Ile Asp Glu Leu	
290 295 300	
agg caa cat ctg ttg aag tgg gga ttt tac aca cca gac aaa aag cat	960
Arg Gln His Leu Leu Lys Trp Gly Phe Tyr Thr Pro Asp Lys Lys His	
305 310 315 320	

cag aaa gaa cca cca ttc ctt tgg atg ggk tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Xaa Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag cct ata gtg ctg cca gaa aar gac agc tgg act	1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tac cca ggg att	1119
Ile Tyr Pro Gly Ile	
370	
<210> 74	
<211> 1116	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1116)	
<223> Portion of HIV Reverse Transcriptase	
<400> 74	
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag gtc ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Val Gly	
1 5 10 15	
ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
tta gag gaa cta aat ttg cca gga aga tgg aaa cca aaa atg ata ggg	144
Leu Glu Glu Leu Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly	
35 40 45	
gga att gga ggt ttt atc aaa gta aaa cag tat gat cag ata ccc ata	192
Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Asp Gln Ile Pro Ile	
50 55 60	
gaa ata tgt gga cat aaa gct att ggt aca gta tta gta gga cct aca	240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr	
65 70 75 80	
cct gtc aac ata att gga aga aac ttg ttg act cag ctt ggt tgc act	288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr	
85 90 95	
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta aca gaa att tgt aca gaa atg gaa aag gaa ggg	432
Lys Ile Lys Ala Leu Thr Glu Ile Cys Thr Glu Met Glu Lys Glu Gly	

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
1000

130	135	140	
aaa att tca aaa att	ggg cct gaa aat	cca tac aat act cca gta ttt	480
Lys Ile Ser Lys Ile	Gly Pro Glu Asn Pro	Tyr Asn Thr Pro Val Phe	
145	150	155 160	
gct ata aag aaa aaa	gac agt act aaa	tgg aga aaa tta gta gat ttc	528
Ala Ile Lys Lys Lys	Asp Ser Thr Lys	Trp Arg Lys Leu Val Asp Phe	
	165	170 175	
aga gaa ctt aat aag	aga act caa gac	ttc tgg gaa gtt caa tta gga	576
Arg Glu Leu Asn Lys	Arg Thr Gln Asp	Phe Trp Glu Val Gln Leu Gly	
	180	185 190	
ata cca cat ccc gca	ggg tta aaa aag	aaa tca gta aca gtc ctg	624
Ile Pro His Pro Ala	Gly Leu Lys Lys	Lys Lys Ser Val Thr Val Leu	
	195	200 205	
gat gtg ggt gat gca	tat ttt tca gtt	ccc tta gat aaa gaa ttc agg	672
Asp Val Gly Asp Ala	Tyr Phe Ser Val	Pro Leu Asp Lys Glu Phe Arg	
	210	215 220	
aag tac act gca ttt	acc ata cct agt	ata aac aat gag aca cca gga	720
Lys Tyr Thr Ala Phe	Thr Ile Pro Ser	Ile Asn Asn Glu Thr Pro Gly	
	225	230 235	
att aga tac cag tac	aat gtg ctt ccc	cag ggg tgg aaa gga tca cca	768
Ile Arg Tyr Gln Gln	Asn Val Leu Pro	Gln Gly Trp Lys Gly Ser Pro	
	245	250 255	
gca ata ttc caa agt	agc atg aca aaa	atc tta gag cct ttt agg aaa	816
Ala Ile Phe Gln Ser	Ser Met Thr Lys	Ile Leu Glu Pro Phe Arg Lys	
	260	265 270	
caa aat cca gac ata	gtt atc tac caa	tac atg gat gat ttg tat gta	864
Gln Asn Pro Asp Ile	Val Ile Tyr Gln	Tyr Met Asp Asp Leu Tyr Val	
	275	280 285	
gga tct gac tta gaa	ata ggg cag cat	aga aca aaa ata gag gaa ctg	912
Gly Ser Asp Leu Glu	Ile Gly Gln His	Arg Thr Lys Ile Glu Glu Leu	
	290	295 300	
aga cag cat ctg ttg	agg tgg gga ttt	acc aca cca gac aaa aag cat	960
Arg Gln His Leu Leu	Arg Trp Gly Phe	Thr Thr Pro Asp Lys Lys His	
	305	310 315	
cag aaa gaa cct cca	ttc ctt tgg atg	ggg tat gag ctc cat cct gat	1008
Gln Lys Glu Pro Pro	Phe Leu Trp Met	Gly Tyr Glu Leu His Pro Asp	
	325	330 335	
aaa tgg aca gta cag	cct ata gtg ctg	cca gaa aag gat agc tgg act	1056
Lys Trp Thr Val Gln	Pro Ile Val Leu	Pro Glu Lys Asp Ser Trp Thr	
	340	345 350	
gtc aat gac ata cag	aag tta gtg gga	aaa tta aat tgg gca agt cag	1104
Val Asn Asp Ile Gln	Lys Leu Val Gly	Lys Lys Leu Asn Trp Ala Ser Gln	
	355	360 365	
att tat gca ggg			1116
Ile Tyr Ala Gly			
370			

<210> 75  
 <211> 819  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(819)  
 <223> Portion of HIV Reverse Transcriptase

<400> 75

ccc att agt cct att gam act gta cca gta aaa tta aag cca gga atg	48
Pro Ile Ser Pro Ile Xaa Thr Val Pro Val Lys Leu Lys Pro Gly Met	
1 5 10 15	
gat ggc cca aaa gtt aaa caa tgg cca tta aca gag gaa aaa ata aaa	96
Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys	
20 25 30	
gca ttg gta gaa att tgt aca gaa atg gaa aag gaa gga aaa att tca	144
Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser	
35 40 45	
aaa att ggg cct gaa aat cca tac aat act cca gta ttt gcc ata aag	192
Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys	
50 55 60	
aaa aag gac agt act aaa tgg aga aaa tta gta gat ttc aga gaa ctt	240
Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu	
65 70 75 80	
aat aar aga act caa gat ttc tgg gaa gtt caa tta gga ata cca cat	288
Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His	
85 90 95	
ccc tca ggg tta aaa aag aay aaa tca gta aca gta ttg gat gtg ggt	336
Pro Ser Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu Asp Val Gly	
100 105 110	
gat gca tat ttt tca gtt ccy tta gat aaa gac ttc agg aag tat act	384
Asp Ala Tyr Phe Ser Val Xaa Leu Asp Lys Asp Phe Arg Lys Tyr Thr	
115 120 125	
gca ttt acc ata cct agt ata aac aat gag aca cca ggg att agr tat	432
Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile Xaa Tyr	
130 135 140	
cag tac aat gtg ctt cca caa gga tgg aaa gga tca cca gca ata ttc	480
Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe	
145 150 155 160	
caa agt agc atg aca aaa atc tta gag cct ttt aga aaa cat aat cca	528
Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys His Asn Pro	
165 170 175	
gac ata gtt atc tat caa tac gtg gat gat ttg tat gta gga tct gac	576
Asp Ile Val Ile Tyr Gln Tyr Val Asp Asp Leu Tyr Val Gly Ser Asp	
180 185 190	
tta gaa ata gag gag cat aga aca aaa ata gag gaa ctg agr vrg cat	624
Leu Glu Ile Glu Glu His Arg Thr Lys Ile Glu Glu Leu Xaa Xaa His	
195 200 205	
ctg tta aag tgg gga ttt acy aca cca gac aaa aag cat cag aaa gaa	672
Leu Leu Lys Trp Gly Phe Xaa Thr Pro Asp Lys Lys His Gln Lys Glu	
210 215 220	
cct cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat aaa tgg aca	720
Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr	
225 230 235 240	
gta cag cct ata aag ctg cca gaa aaa gac agc tgg act gtc aat gac	768







taa Leu	aat Asn	ttt Phe	cct Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aaag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aag Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gag Glu	aag Lys	gaa Glu	ggg Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gct Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	aac Asn	agt Ser	act Thr	aga Arg	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	acg Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	nnn Xaa	nnn Xaa	576
nnn Xaa	nnn Xaa	nnn Xaa 195	nnn Xaa	nnn Xaa	ggg Gly	twa Xaa 200	aaa Lys	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gta Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	cct Pro	cta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	aga Arg	672
aag Lys 225	tac Tyr	act Thr	gca Ala	ttc Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctg Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr 265	aaa Lys	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gtg Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	caa Gln	cat His	ttg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggg Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val 345	ctg Leu	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056
gtc Val	aat Asn	gac Asp	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp	gca Ala	agc Ser	cag Gln	1104



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400

Asp	Phe	Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Xaa	Glu	Val	Gln	
			180					185					190			
tta	gga	ata	cca	cat	ccc	gca	ggg	tta	aag	aag	aaa	aaa	tca	gya	aca	624
Leu	Gly	Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Xaa	Thr	
			195				200					205				
rta	ttg	gat	gtg	ggg	gat	gca	tat	ttt	tca	ggt	ccc	tta	gat	raa	gac	672
Xaa	Leu	Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Xaa	Asp	
	210					215					220					
ttc	agg	aag	tat	act	gca	ttt	acc	ata	cct	agt	ata	aac	aat	gag	aca	720
Phe	Arg	Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	
	225				230					235					240	
cca	ggg	att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	768
Pro	Gly	Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	
				245				250						255		
tca	cca	gct	ata	ttc	caa	agt	agc	atg	aca	aaa	atc	tta	gag	cct	ttt	816
Ser	Pro	Ala	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	
			260					265					270			
aga	aaa	caa	aat	cca	gay	ata	gtt	atc	tat	caa	tac	atg	gat	gat	ttg	864
Arg	Lys	Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	
		275					280					285				
tat	gta	gga	tct	gay	tta	gaa	ata	gag	cag	cat	aga	ata	aaa	ata	gag	912
Tyr	Val	Gly	Ser	Asp	Leu	Glu	Ile	Glu	Gln	His	Arg	Ile	Lys	Ile	Glu	
	290					295					300					
gaa	ctg	aga	caa	yat	ytg	tgg	arg	tgg	ggr	ttt	tac	aca	cca	gac	aaa	960
Glu	Leu	Arg	Gln	Xaa	Xaa	Trp	Xaa	Trp	Xaa	Phe	Tyr	Thr	Pro	Asp	Lys	
	305				310				315						320	
aaa	cat	cag	aaa	gaa	cct	cca	ttc	cat	tgg	atg	ggt	tat	gaa	ctc	cat	1008
Lys	His	Gln	Lys	Glu	Pro	Pro	Phe	His	Trp	Met	Gly	Tyr	Glu	Leu	His	
				325					330					335		
cct	gat	aaa	tgg	aca	gta	cag	cct	ata	gtg	ctg	cca	gaa	aaa	gac	agc	1056
Pro	Asp	Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	
			340				345						350			
tgg	act	gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	ttg	aat	tgg	gca	1104
Trp	Thr	Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	
		355				360						365				
agt	cag	att	tat	gca	ggr											1122
Ser	Gln	Ile	Tyr	Ala	Xaa											
		370														

<210> 79  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)  
  
 <220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease  
  
 <221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase  
  
 <400> 79

cct	cag	atc	act	ctt	tgg	caa	cga	ccc	ctc	gtt	aca	ata	aag	gta	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Ile	Lys	Val	Gly	
1				5					10					15		
ggg	caa	cta	aag	gaa	gct	cta	tta	gat	aca	gga	gca	gac	aat	aca	gta	96
Gly	Gln	Leu	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asn	Thr	Val	
			20					25					30			
ttc	gaa	gac	ctg	gat	tta	cca	gga	agg	tgg	aaa	cca	aaa	atg	ata	ggg	144
Phe	Glu	Asp	Leu	Asp	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	
		35					40					45				
gga	att	gga	ggt	ttt	atc	aaa	gta	aaa	cag	tat	gag	cag	ata	ccc	ata	192
Gly	Ile	Gly	Gly	Phe	Ile	Lys	Val	Lys	Gln	Tyr	Glu	Gln	Ile	Pro	Ile	
	50					55					60					
gaa	atc	tgt	ggg	cgt	aaa	gct	ata	ggt	aca	gtg	tta	gta	gga	cct	aca	240
Glu	Ile	Cys	Gly	Arg	Lys	Ala	Ile	Gly	Thr	Val	Leu	Val	Gly	Pro	Thr	
65					70					75					80	
cct	gtc	aac	ata	att	gga	aga	gat	ctg	ttg	act	cag	att	ggt	tgc	act	288
Pro	Val	Asn	Ile	Ile	Gly	Arg	Asp	Leu	Leu	Thr	Gln	Ile	Gly	Cys	Thr	
				85					90					95		
cta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aga	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Arg	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	ata	gaa	att	tgt	gca	gaa	atg	gaa	aag	gaa	ggg	432
Lys	Ile	Lys	Ala	Leu	Ile	Glu	Ile	Cys	Ala	Glu	Met	Glu	Lys	Glu	Gly	
	130					135					140					
aaa	att	tca	aaa	att	ggg	cct	gaa	aat	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aag	aac	agt	aat	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asn	Ser	Asn	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aag	aga	act	caa	gac	ttc	tgg	gaa	gtt	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aaa	aag	tca	ata	aca	gta	tta	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Ile	Thr	Val	Leu	
		195					200					205				
gat	gtg	ggt	gat	gca	tat	ttc	tca	gtt	ccc	tta	gat	gaa	gac	ttc	agg	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Glu	Asp	Phe	Arg	
	210					215					220					
aag	tat	act	gca	ttt	acc	ata	cct	agt	aca	aac	aat	gag	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Thr	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
att	aga	tat	cag	tac	aat	gtg	ctg	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
			245						250					255		
gca	ata	ttc	caa	agt	agc	atg	aca	aaa	att	tta	gag	cct	ttt	aga	aaa	816
Ala	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			



85								90				95						
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336		
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384		
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aar Lys	gaa Glu	ggg Gly	432		
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	rta Xaa	ttt Phe 160	480		
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528		
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	agg Arg	act Thr	caa Gln	gat Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576		
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	ttg Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624		
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	aga Arg	672		
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720		
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768		
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816		
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtc Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864		
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	agg Arg	aca Thr	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912		
aga Arg 305	caa Gln	cat His	ttg Leu	ttg Leu	aag Lys 310	tgg Trp	ggg Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960		
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggg Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008		
aaa Lys	tgg Trp	aca Thr	gtg Val 340	cag Gln	cct Pro	ata Ile	gtg Val	tta Leu 345	ccg Pro	gaa Glu	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056		
gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	ttg	aat	tgg	gca	agt	caq	1104		

Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
 355 360 365

att tac cca ggg att 1119  
 Ile Tyr Pro Gly Ile  
 370

<210> 81  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400> 81  
 cct caa atc act ctt tgg caa cga ccy ctt gtt rcc ata aag ata ggg 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Xaa Leu Val Xaa Ile Lys Ile Gly  
 1 5 10 15  
 ggg caa cta arg gaa gct cta tta gat aca gga gca gat gat aca gta 96  
 Gly Gln Leu Xaa Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
 20 25 30  
 tta gaa gaa ata aat ttg cca gga aga tgg aaa cca aaa atg ata ggg 144  
 Leu Glu Glu Ile Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly  
 35 40 45  
 gga att gga ggt ttt atc aaa gta aaa cag tat gat caa ata ccy rta 192  
 Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Asp Gln Ile Xaa Xaa  
 50 55 60  
 gaa att tgt gga cat aga gct ata ggt aca gtw tta gta gga cct aca 240  
 Glu Ile Cys Gly His Arg Ala Ile Gly Thr Xaa Leu Val Gly Pro Thr  
 65 70 75 80  
 cct gtc aac ata att gga agr aat ctg ttg act cag att ggt tgc act 288  
 Pro Val Asn Ile Ile Gly Xaa Asn Leu Leu Thr Gln Ile Gly Cys Thr  
 85 90 95  
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
 100 105 110  
 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
 115 120 125  
 aaa ata aaa gca ttg gta gaa att tgt aca gaa atg gaa aag gaa gga 432  
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly  
 130 135 140  
 aaa att tca aga att ggg cct gaa aat cca tac aat act cca gta ttt 480  
 Lys Ile Ser Arg Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
 145 150 155 160  
 gct ata aag aaa aar gat agt act aaa tgg aga aaa tta gta gat ttc 528  
 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
 165 170 175











gtc aat gac ata cag aaa tta gta gga aaa tta aat tgg gca agt cag	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tat cca ggg	1116
Ile Tyr Pro Gly	
370	
<210> 84	
<211> 1116	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1116)	
<223> Portion of HIV Reverse Transcriptase	
<400> 84	
cct caa atc act ctt tgg caa cga ccc att gtc aca ata aaa gta ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Val Gly	
1 5 10 15	
ggg caa cta atg gaa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Met Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	
tta gaa gac ata aat ttg cca gga aga tgg aaa cca aaa ata ata ggg	144
Leu Glu Asp Ile Asn Leu Pro Gly Arg Trp Lys Pro Lys Ile Ile Gly	
35 40 45	
gga att ggt ggt ttt gtc aaa gtg aga cag tat gat cag gta ccc ata	192
Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Val Pro Ile	
50 55 60	
gaa atc tgt gga cat aaa gtt ata ggt aca gta tta gta gga cct aca	240
Glu Ile Cys Gly His Lys Val Ile Gly Thr Val Leu Val Gly Pro Thr	
65 70 75 80	
cct acc aac gta gtt gga aga aat ctg atg act cag att ggc tgc acy	288
Pro Thr Asn Val Val Gly Arg Asn Leu Met Thr Gln Ile Gly Cys Xaa	
85 90 95	
tta aat ttt cct att agt cct att gaa act gta cca gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg acg gaa gaa	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta gta gaa att tgt aca gaa ctg gaa aag gat gga	432
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Asp Gly	
130 135 140	
aaa att tca aaa att ggg cct gaa aat cca tat aat act cca ata ttt	480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe	
145 150 155 160	
gcc ata aag aaa aag aac agt gat aaa tgg aga aaa tta gta gat ttc	528
Ala Ile Lys Lys Lys Asn Ser Asp Lys Trp Arg Lys Leu Val Asp Phe	
165 170 175	



<400> 85	
cct caa atc act ctt tgg caa cga ccc ctc gtc aca ata aaa gta ggg Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Val Gly 1 5 10 15	48
ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val 20 25 30	96
tta gaa gaa atg aat ttg cca ggg aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta agc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Ser Ile 50 55 60	192
gaa atc tgt gga cat aaa gct ata ggt aca gta tta ata gga ccc acc Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga aat ctg ttg act cag ctt ggt tgc act Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aga gtt aaa caa tgg cca ttg aca gaa gaa Pro Gly Met Asp Gly Pro Arg Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt aca gaa atg gag aag gaa ggr Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Xaa 130 135 140	432
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480
gcc ata aar aaa aaa gac agt act aaa tgg aga aag tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 170 175	528
aga gaa ctt aat aaa ara act caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Xaa Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 180 185 190	576
ata cca cat ccc gca ggg tta aaa aag aam aaa tca gta aca gta ctg Ile Pro His Pro Ala Gly Leu Lys Lys Xaa Lys Ser Val Thr Val Leu 195 200 205	624
gay gtg ggt gat gcr tat ttt tca gtt ccy tta gay aaa gay ttc agg Asp Val Gly Asp Xaa Tyr Phe Ser Val Xaa Leu Asp Lys Asp Phe Arg 210 215 220	672
aag tac aca gca ttt acc ata cct agt gta aac aat gag rca cca ggg Lys Tyr Thr Ala Phe Thr Ile Pro Ser Val Asn Asn Glu Xaa Pro Gly 225 230 235 240	720
att aga tat cag tac aat gtg ctt cca car gga tgg aaa gga tca cca Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aar Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	816

260	265	270	
maa aat cca gac ata gty atc tay	caa tac atg gat gat ttr tat gta	864	
Xaa Asn Pro Asp Ile Xaa Ile Tyr	Gln Tyr Met Asp Asp Xaa Tyr Val		
275	280 285		
gga tct gac tta gaa ata gga cag cat aga aca aaa ata gag gaa ctg	912		
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu			
290	295 300		
aga caa cat ctg ttg cag tgg ggg tta acc aca cca gac aaa aaa cat	960		
Arg Gln His Leu Leu Gln Trp Gly Leu Thr Thr Pro Asp Lys Lys His			
305	310 315 320		
cag aaa gaa cct cca ttc ctt tgg atg ggg tat gaa ctc cat ccg gat	1008		
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			
	325 330 335		
aaa tgg aca gta cag cct ata wtg ctg cca gac aaa gac agc tgg act	1056		
Lys Trp Thr Val Gln Pro Ile Xaa Leu Pro Asp Lys Asp Ser Trp Thr			
	340 345 350		
gtm aat gac ata cag aar tta gta gga aaa ttg aat tgg gcg agt cag	1104		
Xaa Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln			
	355 360 365		
atc tac cca ggg	1116		
Ile Tyr Pro Gly			
	370		
<210> 86			
<211> 1116			
<212> DNA			
<213> Human Immunodeficiency Virus (HIV)			
<220>			
<221> CDS			
<222> (0)...(297)			
<223> HIV Protease			
<221> CDS			
<222> (298)...(1116)			
<223> Portion of HIV Reverse Transcriptase			
<400> 86			
cct caa atc act ctt tgg caa cga ccc atc gtc aca gta aag ata ggg	48		
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Val Lys Ile Gly			
1	5 10 15		
ggg cac aca acg gaa gct cta tta gat aca gga gca gat gat aca gta	96		
Gly His Thr Thr Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val			
	20 25 30		
tta gaa gaa atg aat ttg cca ggg aga tgg aaa cca aaa atg ata gga	144		
Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly			
	35 40 45		
gga att gga ggt ttt atc aaa gta aga cag tat gag cag gta ccc ata	192		
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Glu Gln Val Pro Ile			
	50 55 60		
gaa ttc tgt gga cat aaa act gta ggt aca gta tta ata gga cct aca	240		
Glu Phe Cys Gly His Lys Thr Val Gly Thr Val Leu Ile Gly Pro Thr			
	65 70 75 80		
cct gtc aac ata att gga aga aat ctg atg act cag att ggt tgt act	288		



Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Met	Thr	Gln	Ile	Gly	Cys	Thr	
85																
tta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
100																
cca	gga	atg	gat	ggg	ccc	aaa	gtt	aaa	cca	tgg	cca	ttg	aca	gaa	aga	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Pro	Trp	Pro	Leu	Thr	Glu	Arg	
115																
aaa	aat	aaa	gca	tta	gta	gaa	att	tgt	tcc	gaa	atg	gaa	aaa	gga	agg	432
Lys	Asn	Lys	Ala	Leu	Val	Glu	Ile	Cys	Ser	Glu	Met	Glu	Lys	Gly	Arg	
130																
aaa	att	tca	aaa	att	ggg	cct	gag	aat	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
145																
gcc	ata	aag	aaa	aag	aac	agt	act	aga	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asn	Ser	Thr	Arg	Trp	Arg	Lys	Leu	Val	Asp	Phe	
165																
aga	gaa	ctt	aat	aaa	aga	act	caa	gac	ttc	tgg	gaa	gtt	cag	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
180																
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aac	aaa	tca	gta	aca	gta	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Asn	Lys	Ser	Val	Thr	Val	Leu	
195																
gat	gta	ggg	gat	gca	tat	ttt	tca	gtt	ccc	tta	gat	gaa	gaa	ttc	agg	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Glu	Glu	Phe	Arg	
210																
aag	tat	act	gca	ttc	acc	ata	cct	agt	aca	aac	aat	gaa	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Thr	Asn	Asn	Glu	Thr	Pro	Gly	
225																
att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
245																
gca	ata	ttc	caa	tgt	agc	atg	aca	aaa	atc	tta	gag	ccc	ttt	aga	aaa	816
Ala	Ile	Phe	Gln	Cys	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
260																
caa	aat	cca	gaa	ata	gtt	atc	tgt	cag	tac	atg	gat	gac	ttg	tat	gta	864
Gln	Asn	Pro	Glu	Ile	Val	Ile	Cys	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
275																
gca	tct	gat	tta	gaa	ata	ggg	cag	cat	aga	aca	aaa	gta	gag	gaa	ctg	912
Ala	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Val	Glu	Glu	Leu	
290																
aga	caa	cat	ctg	ttg	aag	tgg	ggg	ttt	ttc	aca	cca	gac	gaa	aaa	cat	960
Arg	Gln	His	Leu	Leu	Lys	Trp	Gly	Phe	Phe	Thr	Pro	Asp	Glu	Lys	His	
305																
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
325																
aaa	tgg	aca	gta	cag	cct	ata	gta	ctg	cca	gac	caa	gac	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Asp	Gln	Asp	Ser	Trp	Thr	
340																
345																

gtc aat gat ata cag aag tta gtg gga aaa tta aat tgg gca agt caa 1104  
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
355 360 365

att tac cca ggg 1116  
Ile Tyr Pro Gly  
370

```
<210> 87
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

```
<220>
<221> CDS
<222> (0) ... (297)
<223> HIV Protease
```

```
<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

```
<400> 87
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata gag      48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Glu
      1           5           10           15
```

ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta 96  
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
20 25 30

tta gaa gaa atg aat ttg tca gga aga tgg aaa cca aaa atg ata ggg 144  
Leu Glu Glu Met Asn Leu Ser Gly Arg Trp Lys Pro Lys Met Ile Gly  
35 40 45

gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata ccc ata 192  
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile  
50 55 60

gag atc tgt gga cat aaa gct gta ggt aca gta tta gta gga cct aca 240  
Glu Ile Cys Gly His Lys Ala Val Gly Thr Val Leu Val Gly Pro Thr  
65 70 75 80

cct gtc aac ata att gga agr aat ctg ttg act cag att ggt tgc acc 288  
Pro Val Asn Ile Ile Gly Xaa Asn Leu Leu Thr Gln Ile Gly Cys Thr  
85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
100 105 110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg 432  
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly  
130 135 140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca ata ttt 480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Ile Phe  
145 150 155 160

gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat tty 528  
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
165 170 175



<400> 88  
cct cag atc act ctt tgg caa cga ccc atc gtc aca ata aag ata ggg 48  
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly  
1 5 10 15

ggg caa cta agg raa gct cta tta gat aca gga gca gat gat aca gta 96  
Gly Gln Leu Arg Xaa Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
20 25 30

tta gaa gac ata gaa ttg cca gga aga tgg aaa cca aaa atg ata ggg 144  
Leu Glu Asp Ile Glu Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly  
35 40 45

gga att gga ggt ttt gtc aaa gta aga caa tat gat cag ata ccc ata 192  
Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile  
50 55 60

gaa atc tgt gga cat aaa gtt ata ggt aca gta tta gta gga cct aca 240  
Glu Ile Cys Gly His Lys Val Ile Gly Thr Val Leu Val Gly Pro Thr  
65 70 75 80

cct gcc aac ata att gga aga aat ctg atg act cag ctt ggt tgc act 288  
Pro Ala Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Leu Gly Cys Thr  
85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
100 105 110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca aaa gaa 384  
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Lys Glu  
115 120 125

aaa ata gaa gca tta atr gaa att tgt gma ttt ttg gaa aag gaa gga 432  
Lys Ile Glu Ala Leu Xaa Glu Ile Cys Xaa Phe Leu Glu Lys Glu Gly  
130 135 140

aaa att tca aaa att ggg cct gaa aat ccg tac aac act cca gta ttt 480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
145 150 155 160

gcc ata aag aaa aaa gga ggt act aaa tgg aga aaa ata gta gat ttc 528  
Ala Ile Lys Lys Lys Gly Gly Thr Lys Trp Arg Lys Ile Val Asp Phe  
165 170 175

aga gaa ctt aat aaa aga act caa gac ttc tgg gaa gtt caa tta gga 576  
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
180 185 190

ata cca cat ccc gcg ggg tta aaa aag aay aaa tca gta aca gta ctg 624  
Ile Pro His Pro Ala Gly Leu Lys Lys Asn Lys Ser Val Thr Val Leu  
195 200 205

gat gtg ggt gat gca tat ttt tca att ccc tta gat gaa gaa ctc agg 672  
Asp Val Gly Asp Ala Tyr Phe Ser Ile Pro Leu Asp Glu Glu Leu Arg  
210 215 220

aag tat act gca ttt act ata cct agt aca aac aat gag aca cca ggg 720  
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Thr Asn Asn Glu Thr Pro Gly  
225 230 235 240

att aga tac caa tac aat gtg ctt cca cag gga tgg aaa gga tca cca 768  
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro  
245 250 255

gca ata ttt caa agt agc atg aca aaa atc tta gag ccc ttt aga aag 816  
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys

caa aat cca gac ata gtt atc twt caw tac gtg gat gat ttg tat gta 864  
 Gln Asn Pro Asp Ile Val Ile Xaa Xaa Tyr Val Asp Asp Leu Tyr Val  
 275 280 285

gga tct gac tta gaa ata ggg aag cat agg gaa aaa ata gag gaa ctg 912  
 Gly Ser Asp Leu Glu Ile Gly Lys His Arg Glu Lys Ile Glu Glu Leu  
 290 295 300

aga caa cat ctg tgg aag tgg gga ttt tac aca cca gac gaa aaa cat 960  
 Arg Gln His Leu Trp Lys Trp Gly Phe Tyr Thr Pro Asp Glu Lys His  
 305 310 315 320

cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat ctt gat 1008  
 Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Leu Asp  
 325 330 335

aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act 1056  
 Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr  
 340 345 350

gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag 1104  
 Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
 355 360 365

att tat gca ggg 1116  
 Ile Tyr Ala Gly  
 370

<210> 89  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400> 89  
 cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly  
 1 5 10 15

ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta 96  
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
 20 25 30

tta gaa gaa atg agt ttg cca ggg aga tgg aaa cca aaa atg ata ggg 144  
 Leu Glu Glu Met Ser Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly  
 35 40 45

gga att gga ggt ttt atc aaa gta aga caa ttt gat cag ata ccc ata 192  
 Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Phe Asp Gln Ile Pro Ile  
 50 55 60

gaa ata tgt gga cac aaa gct ata ggt aca gta tta ata gga cct aca 240  
 Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr  
 65 70 75 80

cct gtc aac ata att gga agg aat ctg ttg act cag ctt ggt tgc act 288

Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Leu	Gly	Cys	Thr	
				85					90					95		
tta	aat	ttt	ccc	atc	agt	cct	att	gaa	cct	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Pro	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gaa	att	tgt	aca	gaa	ctg	gaa	aaa	gaa	ggg	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Leu	Glu	Lys	Glu	Gly	
	130					135					140					
aaa	att	tca	aaa	att	ggg	cct	gaa	aat	cca	tac	aat	act	cca	ata	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Ile	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aaa	gac	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asp	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctg	aat	aag	aaa	act	caa	gac	ttc	tgg	gaa	gtt	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Lys	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	ccc	gca	ggg	tta	aaa	aag	aaa	aaa	tca	gta	acg	gta	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu	
		195				200						205				
gat	gtg	ggt	gat	gca	tat	ttt	tca	gtt	ccc	tta	gat	aaa	gac	ttc	agg	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Lys	Asp	Phe	Arg	
	210					215					220					
aaa	tat	act	gca	ttt	acc	ata	cct	agt	aca	aac	aat	gag	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Thr	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
att	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
			245						250					255		
gca	ata	ttt	caa	cat	agc	atg	aca	aaa	atc	tta	gag	cct	ttt	aga	aaa	816
Ala	Ile	Phe	Gln	His	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			
cag	aat	cca	gac	ata	gtt	atc	tat	caa	tac	gtg	gat	gac	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Val	Asp	Asp	Leu	Tyr	Val	
		275					280				285					
gga	tct	gac	tta	gaa	ata	ggg	cag	cat	aga	aca	aaa					

gtc aat gat ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag 1104  
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
355 360 365

att tat gca ggg 1116  
ile Tyr Ala Gly  
370

```
<210> 90
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

```
<220>
<221> CDS
<222> (0) ... (297)
<223> HIV Protease
```

```
<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 90  
cct cag atc act ctt tgg caa cga ccc aty gtc aca ata aaa gta ggg 48  
Pro Gln Ile Thr Leu Trp Gln Arg Pro Xaa Val Thr Ile Lys Val Gly  
1 5 10 15

gga cag cta aag gaa gct yta tta gat aca gga gca gat gat aca gta 96  
Gly Gln Leu Lys Glu Ala Xaa Leu Asp Thr Gly Ala Asp Asp Thr Val  
20 25 30

tta	gaa	gaa	atg	aac	ttg	cca	gga	aaa	tgg	aaa	cca	aaa	ata	ata	ggg	144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Lys	Trp	Lys	Pro	Lys	Ile	Ile	Gly	
		35					40					45				

gga att gga ggt ttt gtc aga gta aga caa tat gat cag gta cct gta 192  
Gly Ile Gly Gly Phe Val Arg Val Arg Gln Tyr Asp Gln Val Pro Val  
50 55 60

gaa att tgt gga cat aaa gct ata ggt tca gta tta gta gga cca aca 240  
Glu Ile Cys Gly His Lys Ala Ile Gly Ser Val Leu Val Gly Pro Thr  
65 70 75 80

cct gcc aac ata att gga aga aat ctg atg act cag ctt ggt ttc act 288  
Pro Ala Asn Ile Ile Gly Arg Asn Leu Met Thr Gln Leu Gly Phe Thr  
85 90 95

tta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
115 120 125

aaa ata aaa gca tta gta gar att tgt aca gaa ytg gaa aaa gaa gga 432  
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Xaa Glu Lys Glu Gly  
130 135 140

aag att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt 480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
145 150 155 160

gcc ata aag aaa aag aac agt gat aga tgg aga aaa tta gta gat ttc 528  
Ala Ile Lys Lys Lys Asn Ser Asp Arg Trp Arg Lys Leu Val Asp Phe  
165 170 175

```

aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga      576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly
      180                               185                               190

ata cca cat cct gga ggg tta aaa aag aaa aaa tca gta aca gta cta      624
Ile Pro His Pro Gly Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu
      195                               200                               205

gat gtg ggt gat gca tat ttc tca gtt ccc tta gat gaa gac ttc agg      672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg
      210                               215                               220

aag tat act gca ttt acc ata cct agt ata aac aat gag aca cca ggg      720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly
      225                               230                               235

att aga tat car tac aat gtg ctt cca cag gga tgg aaa gga tca cca      768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro
      245                               250                               255

gca ata tty caa agt agc atg aca aaa atc tta gag cct ttt agg aag      816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys
      260                               265                               270

maa aat cca gac ata gtt atc att caa tac atg gat gat ttg tat gtr      864
Xaa Asn Pro Asp Ile Val Ile Ile Gln Tyr Met Asp Asp Leu Tyr Xaa
      275                               280                               285

gga tct gat tta gaa ata gar cag cay aga aca aaa ata gag gaa ctg      912
Gly Ser Asp Leu Glu Ile Glu Gln His Arg Thr Lys Ile Glu Glu Leu
      290                               295                               300

aga gat cat tta ttg agg tgg ggg ttt ttc aca cca gaa caa aaa cat      960
Arg Asp His Leu Leu Arg Trp Gly Phe Phe Thr Pro Glu Gln Lys His
      305                               310                               315

cag aaa gaa cct cca ttc cat tgg atg ggt tat gaa ctc cat cct gat      1008
Gln Lys Glu Pro Pro Phe His Trp Met Gly Tyr Glu Leu His Pro Asp
      325                               330                               335

aaa tgg aca gta cat cct ata gtg ctg cca gaa aaa gac agc tgg act      1056
Lys Trp Thr Val His Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr
      340                               345                               350

gtc aat gac ata cag aag tta gtg gga aaa ttr aat tgg gca agt cag      1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Xaa Asn Trp Ala Ser Gln
      355                               360                               365

att tat gca ggg
Ile Tyr Ala Gly
      370

```

```

<210> 91
<211> 1115
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

```

```

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

```

```

<221> CDS
<222> (298)...(1115)
<223> Portion of HIV Reverse Transcriptase

```



<400>	91																
cct	cag	atc	act	ctt	tgg	caa	cga	ccc	ctt	gtc	aca	gta	aag	ata	ggg		48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Val	Lys	Ile	Gly		
1				5					10					15			
ggg	caa	cta	ata	gaa	gct	cta	tta	gat	aca	gga	gca	gat	gat	aca	gta		96
Gly	Gln	Leu	Ile	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val		
			20					25					30				
ttg	gaa	gaa	atg	aat	ttg	cca	ggg	aga	tgg	aaa	cca	aaa	ata	ata	ggg		144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Ile	Ile	Gly		
			35				40					45					
gga	att	gga	ggt	ttt	atc	aaa	gta	aga	cag	tat	gat	cag	ata	ccc	ata		192
Gly	Ile	Gly	Gly	Phe	Ile	Lys	Val	Arg	Gln	Tyr	Asp	Gln	Ile	Pro	Ile		
	50					55					60						
gaa	atc	tgt	gga	cat	aaa	gtt	ata	rgt	cca	gta	tta	ata	gga	cct	aca		240
Glu	Ile	Cys	Gly	His	Lys	Val	Ile	Xaa	Pro	Val	Leu	Ile	Gly	Pro	Thr		
	65				70					75					80		
cct	gtc	aac	ata	att	gga	aga	aat	ttg	atg	act	cag	att	ggc	tgc	act		288
Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Met	Thr	Gln	Ile	Gly	Cys	Thr		
				85					90					95			
tta	aat	ttt	ccc	atc	agt	cct	att	raa	act	gta	cca	gta	aaa	tta	aag		336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Xaa	Thr	Val	Pro	Val	Lys	Leu	Lys		
			100					105					110				
cca	gga	atg	gat	ggc	cca	aag	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa		384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu		
			115				120					125					
aaa	ata	aaa	gca	tta	gta	gaa	att	tgt	aca	gaa	atg	gaa	aag	gaa	gga		432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly		
	130					135					140						
aaa	atc	tca	aaa	att	ggg	cct	gaa	aac	cca	tac	aat	act	cca	gta	ttt		480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe		
	145				150					155					160		
gcc	ata	aag	aaa	aaa	aac	agt	act	aga	tgg	aga	aaa	tta	gta	gat	ttc		528
Ala	Ile	Lys	Lys	Lys	Asn	Ser	Thr	Arg	Trp	Arg	Lys	Leu	Val	Asp	Phe		
				165					170					175			
aga	gaa	ctt	aat	aag	aga	act	caa	gac	ttc	tgg	gaa	gtt	caa	tta	gga		576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly		
			180					185					190				
ata	cca	cat	cct	gga	ggg	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	ctg		624
Ile	Pro	His	Pro	Gly	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Le		

				260				265				270											
caa	aat	cca	gac	ata	gtt	atc	tat	caa	tac	gtg	gat	gat	ttg	tat	gta					864			
Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Val	Asp	Asp	Leu	Tyr	Val								
275								280				285											
gga	tct	gac	cta	gaa	ata	ggg	cag	cat	aga	aca	aaa	ata	gag	gaa	ctg					912			
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu								
290								295				300											
aga	caa	cat	ttg	ttg	aaa	tgg	gga	ttt	atc	aca	cca	gat	gaa	aaa	cat					960			
Arg	Gln	His	Leu	Leu	Lys	Trp	Gly	Phe	Ile	Thr	Pro	Asp	Glu	Lys	His								
305								310				315				320							
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gat					1008			
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp								
				325				330				335											
aag	tgg	aca	gta	cag	cct	ata	gta	ctg	cca	gaa	aaa	gac	agc	tgg	act					1056			
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr								
				340				345				350											
gtc	aat	gac	ata	cag	aaa	tta	gtg	gga	aaa	ttg	aat	tgg	gca	agt	cag					1104			
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Ser	Gln								
				355				360				365											
att	tat	gca	gg																	1115			
Ile	Tyr	Ala																					
370																							
<210> 92																							
<211> 1116																							
<212> DNA																							
<213> Human Immunodeficiency Virus (HIV)																							
<220>																							
<221> CDS																							
<222> (0)...(297)																							
<223> HIV Protease																							
<221> CDS																							
<222> (298)...(1116)																							
<223> Portion of HIV Reverse Transcriptase																							
<400> 92																							
cct	cag	atc	act	ctt	tgg	caa	cga	ccc	ctc	gtc	aca	ata	aag	ata	ggg					48			
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Ile	Lys	Ile	Gly								
1					5					10					15								
ggg	cag	cta	aag	gaa	gct	cta	tta	gat	aca	gga	gca	gat	gat	aca	gta					96			
Gly	Gln	Leu	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val								
				20					25					30									
tta	gaa	gac	ata	aac	ttg	cca	gga	aaa	tgg	aaa	cca	aaa	atg	ata	ggg					144			
Leu	Glu	Asp	Ile	Asn	Leu	Pro	Gly	Lys	Trp	Lys	Pro	Lys	Met	Ile	Gly								
				35					40					45									
gga	att	gga	ggt	ttt	atc	aaa	gta	aga	cag	tat	gag	cag	gta	ccc	ata					192			
Gly	Ile	Gly	Gly	Phe	Ile	Lys	Val	Arg	Gln	Tyr	Glu	Gln	Val	Pro	Ile								
				50					55					60									
gaa	atc	tgt	gga	cat	aaa	act	ata	ggt	aca	gta	tta	gta	gga	cct	aca					240			
Glu	Ile	Cys	Gly	His	Lys	Thr	Ile	Gly	Thr	Val	Leu	Val	Gly	Pro	Thr								
				65					70					75					80				
cct	gtc	aac	ata	att	gga	aga	aat	ctg	atg	act	cag	att	ggg	tgc	act					288			

Pro	Val	Asn	Ile	Ile 85	Gly	Arg	Asn	Leu	Met 90	Thr	Gln	Ile	Gly	Cys 95	Thr	
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	ggg Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aag Lys 165	aac Asn	agt Ser	act Thr	aga Arg	tgg Trp 170	aga Arg	aaa Lys	gta Val	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aac Asn	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggg Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	acg Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	ata Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ctg Leu	gtt Val	atc Ile	tgt Cys 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	tta Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	cta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gaa Glu	gaa Glu	ctg Leu	912
agg Arg 305	caa Gln	cat His	ctg Leu	ttg Leu	aag Lys 310	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr 315	cca Pro	gac Asp	gaa Glu	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggg Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	ccc Pro	ata Ile	gtg Val 345	ctg Leu	cca Pro	gac Asp	aaa Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056

gtc aat gac ata cag aag tta gtg gga aaa ttg aat tgg gca agt cag 1104  
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln  
355 360 365

att tat gca ggg 1116  
Ile Tyr Ala Gly  
370

<210> 93  
<211> 1116  
<212> DNA  
<213> Human Immunodeficiency Virus (HIV)

<220>  
<221> CDS  
<222> (0)...(297)  
<223> HIV Protease

<221> CDS  
<222> (298)...(1116)  
<223> Portion of HIV Reverse Transcriptase

<400> 93  
cct cag atc act ctt tgg caa cga ccc atc gtc aca ata aag ata gga 48  
Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly  
1 5 10 15

ggg cag cta aag gaa gct cta ata gat aca gga gca gat gat aca gta 96  
Gly Gln Leu Lys Glu Ala Leu Ile Asp Thr Gly Ala Asp Asp Thr Val  
20 25 30

tta gaa gaa atg aat tta cca gga aga tgg aca cca aaa ata ata ggg 144  
Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Thr Pro Lys Ile Ile Gly  
35 40 45

gga att gga ggt ttt gtc aga gta aga cag tat gaa cag ata ccc gta 192  
Gly Ile Gly Gly Phe Val Arg Val Arg Gln Tyr Glu Gln Ile Pro Val  
50 55 60

gaa atc tgc ggg cat aaa gct gta ggt aca gta tta gta gga cct aca 240  
Glu Ile Cys Gly His Lys Ala Val Gly Thr Val Leu Val Gly Pro Thr  
65 70 75 80

cct gcc aac ata att gga aga aat ctg ttg act cag att ggc tgt act 288  
Pro Ala Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr  
85 90 95

tta aat ttt ccc att agt cct att gat act gta cca gta aaa tta aag 336  
Leu Asn Phe Pro Ile Ser Pro Ile Asp Thr Val Pro Val Lys Leu Lys  
100 105 110

cca gga atg gat ggc cca ara gtt aaa caa tgg cca ttg aca gaa gag 384  
Pro Gly Met Asp Gly Pro Xaa Val Lys Gln Trp Pro Leu Thr Glu Glu  
115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa ctg gaa aag gam gga 432  
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Xaa Gly  
130 135 140

aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt 480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
145 150 155 160

gct ata aag aaa aaa gac agt act aaa tgg aga aaa gta gta gat ttc 528  
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Val Val Asp Phe  
165 170 175

[illegible]

```
<210> 94
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 94																	
cct Pro 1	cag Gln	atc Ile	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ctc Leu 10	gtc Val	aca Thr	ata Ile	aag Lys	ata Ile 15	ggg Gly	48	
ggg Gly																	
caa Gln	cta Leu	ata Ile 20	gag Glu	gct Ala	cta Leu	ttg Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val	96		
tta Leu																	
gaa Glu	gaa Glu 35	atg Met	gat Asp	ttg Leu	cca Pro	gga Gly 40	aga Arg	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	ata Ile	ata Ile	ggg Gly	144		
gga Gly																	
att Ile 50	gga Gly	ggt Gly	tgg Trp	atc Ile	aaa Lys 55	gta Val	aga Arg	caa Gln	tat Tyr	gat Asp 60	cag Gln	ata Ile	ccc Pro	ata Ile	192		
gaa Glu 65																	
att Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gtt Val	ata Ile	agt Ser	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240		
cca Pro																	
gtc Val	aac Asn	gta Val	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	atg Met 90	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288		
tta Leu																	
aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336		
cca Pro																	
gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aga Arg	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384		
aag Lys																	
ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu 140	ttg Leu	gaa Glu	aag Lys	gat Asp	ggg Gly	432		
aaa Lys 145																	
att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480		
gcc Ala																	
ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	gta Val	gta Val	gat Asp 175	ttc Phe	528		
aga Arg																	
gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	ggg Gly	576		
ata Ile																	
cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	cca Pro 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624		
gat Asp																	
gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttc Phe	agg Arg	672		
aaa Lys 225																	
tat Tyr	act Thr	gca Ala	ttt Phe 230	acc Thr	ata Ile	cct Pro	agt Ser	ata Ile	aat Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	gga Gly 240	720		
gtt Val																	
aga Arg	tat Tyr	cag Gln	tac Tyr 245	aat Asn	gtg Val	ctc Leu	cca Pro	cag Gln 250	ggg Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768		
gca Ala																	
ata Ile	ttc Phe	caa Gln	agt Ser	agc Ser	atg Met	acc Thr	aaa Lys	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe	aga Arg	aaa Lys	816		

260								265				270					
cag	aat	cca	aac	ata	ctt	att	tgt	caa	tac	atg	gat	gat	ttg	tat	gta	864	
Gln	Asn	Pro	Asn	Ile	Leu	Ile	Cys	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val		
275								280				285					
gga	tct	gac	tta	gaa	ata	gaa	cag	cat	aga	aca	aaa	ata	gag	gaa	ctg	912	
Gly	Ser	Asp	Leu	Glu	Ile	Glu	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu		
290								295				300					
aga	caa	cat	ctg	tgg	aga	tgg	ggg	ttt	tac	aca	cca	gat	aaa	aaa	cat	960	
Arg	Gln	His	Leu	Trp	Arg	Trp	Gly	Phe	Tyr	Thr	Pro	Asp	Lys	Lys	His		
305								310				315					320
cag	aag	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gat	1008	
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp		
325								330				335					
aaa	tgg	aca	gta	cag	cct	ata	gag	ctg	cca	gaa	aaa	gac	agc	tgg	act	1056	
Lys	Trp	Thr	Val	Gln	Pro	Ile	Glu	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr		
340								345				350					
gtc	aat	gat	ata	cag	aag	tta	gtg	gga	aaa	ttg	aat	tgg	gca	agy	cag	1104	
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Xaa	Gln		
355								360				365					
att	tat	gca	ggg													1116	
Ile	Tyr	Ala	Gly														
370																	

```
<210> 95
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 95																
cct	cag	atc	act	ctt	tgg	caa	cga	ccc	ctc	gtc	aca	ata	aag	ata	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Ile	Lys	Ile	Gly	
1				5					10					15		
ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta																96
Gly	Gln	Leu	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
tta gaa gaa atg aat ttg cca gga agg tgg aaa cca aaa atg ata ggg																144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	
		35					40					45				
gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata tcc gta																192
Gly	Ile	Gly	Gly	Phe	Ile	Lys	Val	Arg	Gln	Tyr	Asp	Gln	Ile	Ser	Val	
	50					55					60					
gaa atc tgt ggr cat aaa gct ata ggt aca gta tta rta gga cct aca																240
Glu	Ile	Cys	Xaa	His	Lys	Ala	Ile	Gly	Thr	Val	Leu	Xaa	Gly	Pro	Thr	
65					70					75					80	
cct gtc aac ata att gga agg aat ttg ttg act caq att qqt tqc act																288

Pro	Val	Asn	Ile	Ile 85	Gly	Arg	Asn	Leu	Leu 90	Thr	Gln	Ile	Gly	Cys 95	Thr	
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	tta Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp 185	ttt Phe	tgg Trp	gar Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	agg Arg	672
aag Lys 225	tac Tyr	act Thr	gca Ala	ttt Phe	act Thr 230	ata Ile	cct Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	caa Gln	tac Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	cag Gln 260	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys 265	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gar Glu	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp	gat Asp 285	ctg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	gaa Glu 295	cag Gln	cat His	aga Arg	ata Ile	aaa Lys 300	ata Ile	gag Glu	gaa Glu	ctg Leu	912
aga Arg 305	cac His	cat His	ctg Leu	ttg Leu	aaa Lys 310	tgg Trp	gga Gly	ttt Phe	wmc Xaa 315	aca Thr	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro 325	ttc Phe	ctt Leu	tgg Trp	atg Met	ggg Gly 330	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu 345	cca Pro	gaa Glu	aar Lys	gac Asp	agc Ser 350	tgg Trp	act Thr	1056











Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Ile	Gly	Cys	Thr	
				85					90					95		
tta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gta	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	ggg	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	ttg	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gaa	ata	tgt	aca	gaa	atg	gaa	aag	gaa	ggg	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly	
	130					135				140						
aaa	att	tca	aaa	att	ggg	cca	gaa	aat	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aaa	gac	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asp	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aag	aga	act	caa	gac	ttc	tgg	gaa	gtt	caa	ttg	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	ccc	gca	gga	tta	aaa	aag	aaa	aaa	tca	gta	aca	gta	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu	
		195					200					205				
gat	gtg	ggg	gat	gca	tat	ttt	tca	gtt	ccc	tta	gat	aaa	gac	ttc	agg	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Lys	Asp	Phe	Arg	
	210					215					220					
aag	tac	act	gca	ttt	acc	ata	cct	agt	ata	aac	aat	gag	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
att	aga	tat	cag	tat	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
			245						250					255		
gca	ata	ttc	caa	agt	agc	atg	aca	aaa	atc	tta	gag	cct	ttt	aga	aaa	816
Ala	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys	
			260					265					270			
caa	aat	cca	gay	ata	gtt	att	tat	caa	tac	atg	gat	gat	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Ile	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
		275					280					285				
gga	tcc	gac	cta	gaa	ata	ggg	cag	cat	aga	aca	aaa	ata	gag	gaa	ctg	912
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Thr	Lys	Ile	Glu	Glu	Leu	
	290					295					300					
aga	caa	cac	ctg	ttg	aag	tgg	ggr	ttt	acc	ack	cca	gac	aaa	aaa	cat	960
Arg	Gln	His	Leu	Leu	Lys	Trp	Xaa	Phe	Thr	Xaa	Pro	Asp	Lys	Lys	His	
	305				310					315					320	
cag	aag	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctc	cat	cct	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
				325					330					335		
aaa	tgg	aca	gta	cag	cct	ata	gta	ctg	cca	gaa	aaa	gat	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Pro	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr	
			340					345					350			









000111-50540250

260	265	270	
caa aat cca gac ata gtt atc tat Gln Asn Pro Asp Ile Val Ile Tyr 275 280	caa tac gtg gat gat ttg tat gta Gln Tyr Val Asp Asp Leu Tyr Val		864
gga tct gac tta gaa ata ggg cag cat aga gca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Ala Lys Ile Glu Glu Leu 290 295 300			912
aga caa cat ctg tgg agg tgg gga ttt tac aca cca gac aaa aaa cat Arg Gln His Leu Trp Arg Trp Gly Phe Tyr Thr Pro Asp Lys Lys His 305 310 315 320			960
cag aag gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cct gat Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp 325 330 335			1008
aaa tgg aca gta cag cct ata arg ttg cca gaa aaa gac agc tgg act Lys Trp Thr Val Gln Pro Ile Xaa Leu Pro Glu Lys Asp Ser Trp Thr 340 345 350			1056
gtc aat gam ata cag aaa tta gtg gga aaa tta aat tgg gcc agt cag Val Asn Xaa Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln 355 360 365			1104
att tck cng gg Ile Xaa Xaa 370			1115
<210> 101			
<211> 1096			
<212> DNA			
<213> Human Immunodeficiency Virus (HIV)			
<220>			
<221> CDS			
<222> (0)...(297)			
<223> HIV Protease			
<221> CDS			
<222> (298)...(1096)			
<223> Portion of HIV Reverse Transcriptase			
<400> 101			
cct car atc act ctt tgg cag acc ccc ctt gtc yca ata agg aka ggg Pro Gln Ile Thr Leu Trp Gln Thr Pro Leu Val Xaa Ile Arg Xaa Gly 1 5 10 15			48
ggr cag yta aag gaa gct tta tta gay aca gra gca gat gat mca gta Xaa Gln Xaa Lys Glu Ala Leu Leu Asp Thr Xaa Ala Asp Asp Xaa Val 20 25 30			96
tta gaa gaa atg tat ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Glu Glu Met Tyr Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45			144
gga att gga ggt ttt atc aag gta aga cag tat gat cag ata ccc ata Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile 50 55 60			192
gaa atc tgt gga cac aaa gct ata ggt aca gta ttg gta gga tct aca Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Ser Thr 65 70 75 80			240
cct gtt aac ata att gga aga aat ctg ttg act cag att ggt tgc acc			288

Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Ile	Gly	Cys	Thr	
				85					90					95		
tta	aat	ttt	ccc	att	agt	tct	att	gaa	act	gta	cca	gta	aga	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Ser	Ile	Glu	Thr	Val	Pro	Val	Arg	Leu	Lys	
			100					105					110			
ccc	gga	atg	gat	ggc	cca	aaa	gtt	aag	caa	tgg	cca	tta	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gaa	att	tgt	aca	gaa	atg	gaa	aag	gaa	ggg	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly	
	130					135					140					
aaa	att	tca	aaa	att	ggg	cct	gaa	aat	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
	145				150					155					160	
gcc	ata	aag	aaa	aag	aac	agt	gat	aga	tgg	aga	aaa	gta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asn	Ser	Asp	Arg	Trp	Arg	Lys	Val	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aag	aga	acc	caa	gac	ttt	tgg	gaa	gtt	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	ccc	gca	ggg	tta	aaa	agg	aga	aaa	tca	gta	aca	gta	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Arg	Arg	Lys	Ser	Val	Thr	Val	Leu	
		195					200					205				
gat	gtg	ggt	gat	gca	tac	ttt	tca	att	ccc	tta	gat	aaa	gaa	ttc	aga	672
Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Ile	Pro	Leu	Asp	Lys	Glu	Phe	Arg	
	210					215					220					
aag	tat	act	gca	ttt	acc	ata	cct	agt	aca	aac	aat	gag	aca	cca	ggg	720
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Thr	Asn	Asn	Glu	Thr	Pro	Gly	
	225				230					235					240	
atc	aga	tat	cag	tac	aat	gtg	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	
				245					250					255		
gca	ata	ttc	caa	agt	agc	atg	aca	aaa	atc	tta	gag	cct	ttt	aga	gaa	816
Ala	Ile	Phe	Gln	Ser	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Glu	
			260					265					270			
cag	aat	cca	gac	atg	gtt	atc	tat	caa	tac	atg	gat	gat	ttg	tat	gta	864
Gln	Asn	Pro	Asp	Met	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	
		275					280					285				
gga	tct	gac	tta	gaa	ata	ggg	cag	cat	aga	gca	aaa	ata	gag	gaa	ctg	912
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Ala	Lys	Ile	Glu	Glu	Leu	
	290					295					300					
aga	caa	cat	ctg	ttg	agg	tgg	gga	tta	ttc	aca	cca	gac	caa	aaa	cat	960
Arg	Gln	His	Leu	Leu	Arg	Trp	Gly	Leu	Phe	Thr	Pro	Asp	Gln	Lys	His	
	305				310					315					320	
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggt	tat	gaa	ctc	cat	ccg	gat	1008
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	
				325					330					335		
aaa	tgg	aca	gta	cag	act	ata	gtg	ctg	cca	gag	aag	gac	agc	tgg	act	1056
Lys	Trp	Thr	Val	Gln	Thr	Ile	Val	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr	
			340					345					350			

gtc aat gac ata cag aag tta gta gga aaa ttg aat tgg g 1096  
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp  
355 360 365

<210> 102  
<211> 1048  
<212> DNA  
<213> Human Immunodeficiency Virus (HIV)

<220>  
<221> CDS  
<222> (0)...(297)  
<223> HIV Protease

<221> CDS  
<222> (298)...(1048)  
<223> Portion of HIV Reverse Transcriptase

<400> 102  
cct cag atc act ctt tgg cag cga ccc tty gtc aca ata aag gta ggg 48  
Pro Gln Ile Thr Leu Trp Gln Arg Pro Phe Val Thr Ile Lys Val Gly  
1 5 10 15

ggg caa cta aag gaa gct cta ttg gat aca gga gca gat gat aca ata 96  
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Ile  
20 25 30

tta gaa gaa atg tgt ttg cca gga aga tgg aaa cca aaa ttg ata ggg 144  
Leu Glu Glu Met Cys Leu Pro Gly Arg Trp Lys Pro Lys Leu Ile Gly  
35 40 45

gga att gga ggt ttt gtc aaa gta aga caa tat gat cag ata ccc ata 192  
Gly Ile Gly Gly Phe Val Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile  
50 55 60

gaa atc tgt gga cat aaa gtt ata ggt aca gta tta gta gga cct aca 240  
Glu Ile Cys Gly His Lys Val Ile Gly Thr Val Leu Val Gly Pro Thr  
65 70 75 80

cct gcc aac ata gtt gga aga aat ctg ttg act cag att ggc tgt act 288  
Pro Ala Asn Ile Val Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr  
85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
100 105 110

cca gga atg gat ggg cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gag aag gat gga 432  
Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Asp Gly  
130 135 140

aaa att tca aaa att ggg cct gaa aat cca tay aat act cca gta ttt 480  
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
145 150 155 160

gcc ata aag aaa aaa aat agt gat aaa tgg aga aaa gta gta gat ttc 528  
Ala Ile Lys Lys Lys Asn Ser Asp Lys Trp Arg Lys Val Val Asp Phe  
165 170 175

aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtc caa tta gga 576  
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
180 185 190

ata Ile	cca Pro	cat His 195	ccc Pro	gga Gly	ggg Gly	tta Leu	rag Xaa 200	aag Lys	aac Asn	aaa Lys	tca Ser	ata Ile 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	att Ile	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttc Phe	aga Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe 230	acc Thr	ata Ile	ccy Xaa	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln 250	gga Gly	tgg Trp	aag Lys	gga Gly	tca Ser 255	cca Pro	768
gcc Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys 265	ata Ile	tta Leu	gag Glu	cct Pro	ttt Phe 270	aga Arg	aag Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	att Ile	atc Ile	gtt Val 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gca Ala	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	aag Lys	gaa Glu	cta Leu	912
aga Arg 305	caa Gln	tat Tyr	ctg Leu	tgg Trp	gag Glu 310	tgg Trp	gga Gly	ttt Phe	tac Tyr	aca Thr 315	cca Pro	gac Asp	aaa Lys	aaa Lys	cat His 320	960
caa Gln	cag Gln	gaa Glu	ccc Pro	cca Pro 325	ttc Phe	ctc Leu	tgg Trp	atg Met	ggg Gly 330	tat Tyr	gag Glu	ctc Leu	cat His	cct Pro 335	gat Asp	1008
aaa Lys	tgg Trp	aca Thr	gta Val 340	cag Gln	cct Pro	ata Ile	gtg Val 345	ctg Leu	cca Pro	gaa Glu	aaa Lys	gac Asp	a			1048

```
<210> 103
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

```
<220>
<221> CDS
<222> (0) ... (297)
<223> HIV Protease
```

```
<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 103																
cct	cag	atc	act	ctt	tgg	caa	cga	ccc	ctc	gtc	aca	ata	arg	rta	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Ile	Xaa	Xaa	Gly	
1				5					10					15		
ggg	cag	cta	aag	gaa	gct	cta	tta	gat	aca	gga	gca	gat	gat	aca	gta	96
Gly	Gln	Leu	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			
tta	gaa	gaa	atg	aat	ttg	cca	gga	aga	tgg	aaa	cca	aaa	atg	ata	ggg	144
Leu	Glu	Glu	Met	Asn	Leu	Pro	Gly	Arg	Trp	Lys	Pro	Lys	Met	Ile	Gly	

			35			40			45									
gga Gly	att Ile	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp	cag Gln	ata Ile	ccc Pro	ata Ile	192		
			50				55				60							
gaa Glu	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys	gct Ala	gaa Glu	ggt Gly	aca Thr	gta Val	tta Leu	gta Val	gga Gly	cct Pro	aca Thr	240		
			65				70				75							
ccg Pro	gtc Val	aac Asn	ata Ile	att Ile	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys	act Thr	288		
				85					90									
tta Leu	aat Asn	ttt Phe	ccc Pro	att Ile	agt Ser	cct Pro	att Ile	gaa Glu	act Thr	gta Val	cca Pro	gta Val	aaa Lys	tta Leu	aag Lys	336		
			100					105										
cca Pro	gga Gly	atg Met	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val	aaa Lys	caa Gln	tgg Trp	cca Pro	ctg Leu	aca Thr	gaa Glu	gaa Glu	384		
			115				120				125							
aaa Lys	ata Ile	aaa Lys	gca Ala	tta Leu	aba Xaa	gaa Glu	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met	gaa Glu	aag Lys	gaa Glu	ggr Xaa	432		
			130				135				140							
aaa Lys	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr	aat Asn	act Thr	ccg Pro	gta Val	ttt Phe	480		
			145				150				155							
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp	ttc Phe	528		
				165					170									
aga Arg	gaa Glu	ctt Leu	aat Asn	aag Lys	aaa Lys	act Thr	caa Gln	gac Asp	ttt Phe	tgg Trp	gaa Glu	gtt Val	caa Gln	tta Leu	gga Gly	576		
			180					185				190						
ata Ile	cca Pro	cac His	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val	aca Thr	gta Val	ctg Leu	624		
			195				200				205							
gat Asp	gtg Val	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp	aaa Lys	gaa Glu	ttc Phe	agg Arg	672		
			210				215				220							
aag Lys	tat Tyr	aca Thr	gca Ala	ttt Phe	acc Thr	ata Ile	cct Pro	agt Ser	aca Thr	aac Asn	aat Asn	gag Glu	aca Thr	ccc Pro	agg Arg	720		
			225				230				235							
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln	gga Gly	tgg Trp	aaa Lys	gga Gly	tcg Ser	cca Pro	768		
				245					250									
gca Ala	ata Ile	ttc Phe	caa Gln	agt Ser	agc Ser	atg Met	aca Thr	aaa Lys	atc Ile	tta Leu	gag Glu	cct Pro	ttt Phe	aga Arg	aaa Lys	816		
			260				265				270							
caa Gln	aat Asn	cca Pro	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr	caa Gln	tat Tyr	gtg Val	gat Asp	gat Asp	ttg Leu	tat Tyr	gta Val	864		
			275				280				285							
gga Gly	tct Ser	gac Asp	tta Leu	gag Glu	ata Ile	ggg Gly	cag Gln	cat His	aga Arg	aca Thr	aaa Lys	ata Ile	gag Glu	gaa Glu	ctg Leu	912		
			290				295				300							
aga saa	cat cat	ctg ctg	ttg ttg	agg agg	tgg tgg	qqa qqa	ttt ttt	acc acc	aca aca	cca cca	qac qac	aaa aaa	aaa aaa	cat cat		960		



[illegible]

- 170 -

<212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400> 105  
 cct cag atc act ctt tgg caa cga ccc ttc gtc gtc gta aag ata ggg 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Pro Phe Val Val Val Lys Ile Gly  
 1 5 10 15

ggg caa cta aag gaa gct cta tta gat aca gga gca gat aat aca gta 96  
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asn Thr Val  
 20 25 30

ttt gaa gac ytg aat ttg cca gga aaa tgg aaa cca aaa atg ata ggg 144  
 Phe Glu Asp Xaa Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly  
 35 40 45

gga att gga ggt ttt atc aaa gta aga cag tat gat cag gta ctt gta 192  
 Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Val Leu Val  
 50 55 60

gaa atc tgt gga caa aaa gct ata ggt aca gta tta ata gga cct aca 240  
 Glu Ile Cys Gly Gln Lys Ala Ile Gly Thr Val Leu Ile Gly Pro Thr  
 65 70 75 80

cct gtc aac ata att gga agg gat ctg ttg act cag att ggt tgc act 288  
 Pro Val Asn Ile Ile Gly Arg Asp Leu Leu Thr Gln Ile Gly Cys Thr  
 85 90 95

tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
 100 105 110

cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
 115 120 125

aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg 432  
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly  
 130 135 140

aar att tca aaa att ggg cct gaa aac cca tac aat act cca gta ttt 480  
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
 145 150 155 160

gcc ata aag aaa aaa gac agt act aar tgg aga aaa tta gta gat ttc 528  
 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
 165 170 175

aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga 576  
 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
 180 185 190

ata cca cat cct gca ggg tta aaa aag aaa aaa tca gta aca gta ctg 624  
 Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu  
 195 200 205

gat gtg ggt gat gca tat ttt tca gtt ccc tta gat gaa gay ttc agg 672  
 Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg



	210				215				220											
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr	ata Ile	cct Pro	agc Ser	ata Ile	aac Asn	aat Asn	gag Glu	aca Thr	cca Pro	gga Gly	720				
				230				235												
att Ile	aga Arg	tat Tyr	cag Gln	tac Tyr	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser	cca Pro	768				
				245				250												
gca Ala	ata Ile	ttc Phe	caa Gln	tgt Cys	agc Ser	atg Met	aca Thr	aaa Lys	atc Ile	tta Leu	gat Asp	cct Pro	ttt Phe	aga Arg	aag Lys	816				
				260				265												
caa Gln	aat Asn	cca Pro	gac Asp	cta Leu	gtt Val	atc Ile	tat Tyr	caa Gln	tac Tyr	rtg Xaa	gat Asp	gac Asp	ttg Leu	tat Tyr	gta Val	864				
				275				280												
gga Gly	tct Ser	gat Asp	tta Leu	gaa Glu	ata Ile	ggg Gly	cag Gln	cat His	aga Arg	aca Thr	aaa Lys	ata Ile	gag Glu	gaa Glu	ctg Leu	912				
				290				295												
aga Arg	car Gln	cat His	ctg Leu	ttg Leu	aag Lys	tgg Trp	gga Gly	ttt Phe	acc Thr	aca Thr	cca Pro	gac Asp	aaa Lys	aar Lys	cat His	960				
				305				310												
cag Gln	aaa Lys	gaa Glu	cct Pro	cca Pro	ttc Phe	ctt Leu	tgg Trp	atg Met	ggt Gly	tat Tyr	gaa Glu	ctc Leu	cat His	cct Pro	gat Asp	1008				
				325				330												
aaa Lys	tgg Trp	aca Thr	gta Val	cag Gln	cct Pro	ata Ile	gtg Val	ctg Leu	cca Pro	gaa Glu	aag Lys	gac Asp	agc Ser	tgg Trp	act Thr	1056				
				340				345												
gtc Val	aat Asn	gac Asp	ata Ile	cag Gln	aag Lys	tta Leu	gtg Val	gga Gly	aaa Lys	ttg Leu	aat Asn	tgg Trp	gca Ala	agt Ser	cag Gln	1104				
				355				360												
att Ile	tac Tyr	cca Pro	ggg Gly													1116				
				370																

```
<210> 106
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)
```

```
<220>
<221> CDS
<222> (0) ... (297)
<223> HIV Protease
```

```
<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 106																	
cct	cag	atc	act	ctt	ngg	caa	cga	ccm	att	gtc	aca	ata	aag	gta	ggg		48
Pro	Gln	Ile	Thr	Leu	Xaa	Gln	Arg	Xaa	Ile	Val	Thr	Ile	Lys	Val	Gly		
1				5					10					15			
ggg	cam	tta	aaa	gaa	gtt	ytt	tta	gat	mma	gga	gca	gat	gat	cma	gta		96
Gly	Xaa	Leu	Lys	Glu	Val	Xaa	Leu	Asp	Xaa	Gly	Ala	Asp	Asp	Xaa	Val		
			20					25					30				
tta	gaa	gaa	atr	gat	ttg	cca	gga	aga	tgg	aaa	cca	aaa	atg	ata	ggg		144

Leu	Glu	Glu 35	Xaa	Asp	Leu	Pro	Gly 40	Arg	Trp	Lys	Pro	Lys 45	Met	Ile	Gly	
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	caa Gln	ata Ile	gtt Val	gta Val	192
gaa Glu 65	atc Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	aca Thr	gta Val 75	tta Leu	gta Val	gga Gly	cct Pro	aca Thr 80	240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	ctt Leu	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aaa Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gag Glu	gaa Glu	384
aaa Lys	ata Ile 130	aaa Lys	gca Ala	ttg Leu	gta Val	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aaa Lys 145	att Ile	tca Ser	aaa Lys	aty Xaa	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
agg Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln 190	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	yta Xaa	aaa Lys 200	aag Lys	aac Asn	aaa Lys	tca Ser 205	gta Val	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttc Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	aaa Lys	gac Asp	ttt Phe	agg Arg	672
aag Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	ccc Pro	agt Ser	ata Ile	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	caa Gln 250	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	agt Ser	agc Ser	atg Met	aca Thr 265	aaa Lys 265	atc Ile	cta Leu	gag Glu	cct Pro	ttt Phe 270	agg Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	ata Ile	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	atg Met	gat Asp 285	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser 290	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly 295	cag Gln	cat His	aga Arg	aca Thr	aaa Lys 300	ata Ile	gaa Glu	gaa Glu	ctg Leu	912



[illegible]

<211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400> 108  
 cct caa atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly  
 1 5 10 15  
 ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gtg 96  
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
 20 25 30  
 tta gaa gaa atg aat ttg cca ggg aaa tgg aag cca aaa atg ata ggg 144  
 Leu Glu Glu Met Asn Leu Pro Gly Lys Trp Lys Pro Lys Met Ile Gly  
 35 40 45  
 gga att gga ggg ttt atc aaa gta agm crg tat gat cag ata ccc ata 192  
 Gly Ile Gly Gly Phe Ile Lys Val Xaa Xaa Tyr Asp Gln Ile Pro Ile  
 50 55 60  
 gaa atc tgt gra cat aaa gct aya ggt aca gta tta ata ggm cct act 240  
 Glu Ile Cys Xaa His Lys Ala Xaa Gly Thr Val Leu Ile Xaa Pro Thr  
 65 70 75 80  
 cct gtc aac ata att gga aga awt ctg atg act cag att ggg tgc act 288  
 Pro Val Asn Ile Ile Gly Arg Xaa Leu Met Thr Gln Ile Gly Cys Thr  
 85 90 95  
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
 100 105 110  
 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gag 384  
 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
 115 120 125  
 aaa ata aaa gca tta gta gaa att tgt aca gaa atg gaa aag gaa ggg 432  
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly  
 130 135 140  
 aag att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt 480  
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
 145 150 155 160  
 gct ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc 528  
 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
 165 170 175  
 aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga 576  
 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
 180 185 190  
 ata cca cat cct gca ggt tta aaa aag aaa aaa tca gta aca gta cta 624  
 Ile Pro His Pro Ala Gly Leu Lys Lys Lys Ser Val Thr Val Leu  
 195 200 205  
 gat gtg ggg gat gca tat ttt tca gtt ccc tta gat gaa aac ttc agg 672

000117-50650/42

Asp	Val	Gly	Asp	Ala	Tyr	Phe	Ser	Val	Pro	Leu	Asp	Glu	Asn	Phe	Arg		
	210					215					220						
aag	tat	act	gca	ttt	acc	ata	cct	agt	ata	aac	aat	gag	aca	cca	ggg	720	
Lys	Tyr	Thr	Ala	Phe	Thr	Ile	Pro	Ser	Ile	Asn	Asn	Glu	Thr	Pro	Gly		
225					230					235					240		
att	aga	tat	cag	tac	aat	gta	ctt	cca	cag	gga	tgg	aaa	gga	tca	cca	768	
Ile	Arg	Tyr	Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro		
				245					250					255			
gca	ata	ttc	caa	tgt	agc	atg	aca	aaa	atc	tta	gag	cct	ttc	aga	aag	816	
Ala	Ile	Phe	Gln	Cys	Ser	Met	Thr	Lys	Ile	Leu	Glu	Pro	Phe	Arg	Lys		
			260					265					270				
caa	aat	cca	gaa	atg	gtt	atc	trc	caa	tac	gtg	gat	gay	ttg	tat	gta	864	
Gln	Asn	Pro	Glu	Met	Val	Ile	Xaa	Gln	Tyr	Val	Asp	Asp	Leu	Tyr	Val		
		275					280					285					
ggg	tct	gac	tta	gaa	ata	ggg	cag	cat	aga	gca	aaa	ata	gag	gaa	ctr	912	
Gly	Ser	Asp	Leu	Glu	Ile	Gly	Gln	His	Arg	Ala	Lys	Ile	Glu	Glu	Xaa		
	290					295					300						
aga	caa	cat	ctg	ttg	agg	tg	gga	ttt	acc	aca	cca	gac	aaa	aaa	cat	960	
Arg	Gln	His	Leu	Leu	Arg	Trp	Gly	Phe	Thr	Thr	Pro	Asp	Lys	Lys	His		
305					310					315					320		
cag	aaa	gaa	cct	cca	ttc	ctt	tgg	atg	ggg	tat	gaa	ctm	cat	cct	gat	1008	
Gln	Lys	Glu	Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Xaa	His	Pro	Asp		
				325					330					335			
aaa	tgg	aca	gtg	cag	cat	ata	gaa	ctg	cca	gaa	caa	gag	agc	tgg	act	1056	
Lys	Trp	Thr	Val	Gln	His	Ile	Glu	Leu	Pro	Glu	Gln	Glu	Ser	Trp	Thr		
			340				345						350				
gtc	aat	gac	ata	cag	aag	tta	gtg	gga	aaa	yta	aat	tgg	gca	agy	cag	1104	
Val	Asn	Asp	Ile	Gln	Lys	Leu	Val	Gly	Lys	Xaa	Asn	Trp	Ala	Xaa	Gln		
		355					360					365					
att	tat	gca	ggg													1116	
Ile	Tyr	Ala	Gly														
	370																

<210> 109  
 <211> 1116  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)  
 <220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease  
 <221> CDS  
 <222> (298)...(1116)  
 <223> Portion of HIV Reverse Transcriptase

<400>	109																
cct	caa	atc	act	ctt	tgg	caa	cga	ccc	atc	gtc	aca	gta	aag	ata	gag	48	
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Ile	Val	Thr	Val	Lys	Ile	Glu		
1				5				10						15			
ggg	cag	cta	aag	gaa	gct	yta	tta	gat	aca	gga	gca	gat	aat	aca	gta	96	
Gly	Gln	Leu	Lys	Glu	Ala	Xaa	Leu	Asp	Thr	Gly	Ala	Asp	Asn	Thr	Val		
			20					25					30				

ttg gam gaa ata aat ttg cca gga aga tgg aaa cca aaa atg ata ggg Leu Xaa Glu Ile Asn Leu Pro Gly Arg Trp Lys Pro Lys Met Ile Gly 35 40 45	144
gga att gra ggt ttt atc aaa gta aam cag tat gat sag ata mcc ata Gly Ile Xaa Gly Phe Ile Lys Val Xaa Gln Tyr Asp Xaa Ile Xaa Ile 50 55 60	192
gac atc tgt gga cat aaa gta ata ggt aca ata tta gta gga cct aca Asp Ile Cys Gly His Lys Val Ile Gly Thr Ile Leu Val Gly Pro Thr 65 70 75 80	240
cct gtc aac ata att gga aga gat ctg ttg act cag att ggc tgc act Pro Val Asn Ile Ile Gly Arg Asp Leu Leu Thr Gln Ile Gly Cys Thr 85 90 95	288
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys 100 105 110	336
cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gar gaa Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu 115 120 125	384
aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gaa aag gaa gga Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly 130 135 140	432
aag att tca aaa att ggg cct gaa aat cca tac aac act cca gta ttt Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe 145 150 155 160	480
gcc ata aag aaa aag gac agt act aaa tgg aga aaa tta gta gat ttc Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe 165 170 175	528
aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly 180 185 190	576
ata cca cat cct gca ggg tta aaa aag aaa aaa tca gta aca gta ctg Ile Pro His Pro Ala Gly Leu Lys Lys Lys Ser Val Thr Val Leu 195 200 205	624
gat gtg ggt gat gca tat tty tca gtt ccc tta gmt aaa gaa tnn nnn Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Xaa Lys Glu Xaa Xaa 210 215 220	672
nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn nnn Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa 225 230 235 240	720
nnn nnn nnn nnn nnn nnn nnn nnn cca cag gga tgg aaa gga tca cca Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Pro Gln Gly Trp Lys Gly Ser Pro 245 250 255	768
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys 260 265 270	816
caa aat cca gaa ata gtt atc tac car tac rtg gat gay ttg ttw gta Gln Asn Pro Glu Ile Val Ile Tyr Gln Tyr Xaa Asp Asp Leu Xaa Val 275 280 285	864
gga tct gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa ctg Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu 290 295 300	912





[illegible]

Figure 1. The effect of the concentration of the *Agrobacterium* suspension on the transformation efficiency of *Agrobacterium* strains. The data are the mean values of three independent experiments. Error bars represent standard deviation.

<400>	111																	
cct Pro 1	cag Gln	atc Ile	act Thr	ctt Leu 5	tgg Trp	caa Gln	cga Arg	ccc Pro	ctc Leu 10	gtc Val	aca Thr	ata Ile	aag Lys	ata Ile 15	ggg Gly			48
ggg Gly	caa Gln	ata Ile	aag Lys 20	gaa Glu	gct Ala	cta Leu	tta Leu	gat Asp 25	aca Thr	gga Gly	gca Ala	gat Asp	gat Asp 30	aca Thr	gta Val			96
tta Leu	gaa Glu	gaa Glu 35	atg Met	agc Ser	ttg Leu	cca Pro	gga Gly 40	aaa Lys	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	atg Met	ata Ile	ggg Gly			144
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	agm Xaa	cag Gln	tat Tyr	gwt Xaa 60	cat His	ata Ile	ccc Pro	ata Ile			192
gaa Glu 65	wtc Xaa	tgt Cys	ggm Xaa	cat His	aaa Lys 70	gct Ala	gaa Glu	ggt Gly	aca Thr	gta Val 75	tta Leu	ata Ile	gga Gly	cct Pro	aca Thr 80			240
cct Pro	gtc Val	aac Asn	ata Ile	att Ile 85	gga Gly	aga Arg	aat Asn	ctg Leu	ttg Leu 90	act Thr	cag Gln	ctt Leu	ggt Gly	tgc Cys 95	act Thr			288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	ata Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val 110	aga Arg	cta Leu	aaa Lys			336
cca Pro	gga Gly	atg Met 115	gat Asp	ggg Gly	cca Pro	aaa Lys	gtt Val 120	aag Lys	caa Gln	tgg Trp	cca Pro	cta Leu 125	aca Thr	gaa Glu	gaa Glu			384
aaa Lys	atc Ile 130	aaa Lys	gca Ala	ttg Leu	ata Ile	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu 140	atg Met	gaa Glu	aag Lys	gaa Glu	gga Gly			432
aaa Lys 145	att Ile	gaa Glu	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160			480
gcc Ala	ata Ile	agg Arg	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe			528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gac Asp 185	ttt Phe	tgg Trp	gaa Glu	att Ile	caa Gln 190	tta Leu	gga Gly			576
ata Ile	cca Pro	cat His 195	ccc Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu			624

gat gtg ggt gat gca tat ttt tca gtt ccc tta gat aaa gac ttc agg	672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Lys Asp Phe Arg	
210 215 220	
aag tat act gca ttt acc ata cct agt gta aat aat gag aca cca gga	720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Val Asn Asn Glu Thr Pro Gly	
225 230 235 240	
att aga tat caa tac aat gtg ctt cca caa gga tgg aaa gga tca cca	768
Ile Arg Tyr Gln Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg aca aaa atc tta gag cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
caa aat cca gaa yta gtt atc tac caa tac atg gat gat ttg tat gta	864
Gln Asn Pro Glu Xaa Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val	
275 280 285	
gga tca gac tta gaa ata gar aag cat aga gca aaa ata gag gaa ctg	912
Gly Ser Asp Leu Glu Ile Glu Lys His Arg Ala Lys Ile Glu Glu Leu	
290 295 300	
aga gaa cat ctg tya aaa tgg ggg ttt acc aca cca gac aaa aaa cat	960
Arg Glu His Leu Xaa Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His	
305 310 315 320	
cag aaa gaa cct cca ttt ctt tgg atg ggt tat gaa ctc cat cct gat	1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp	
325 330 335	
aaa tgg aca gta cag acc ata aag ctg cca gaa aaa gac agc tgg act	1056
Lys Trp Thr Val Gln Thr Ile Lys Leu Pro Glu Lys Asp Ser Trp Thr	
340 345 350	
gtc aat gat ata cag aag tta gtg gga aaa ttg aat tgg gca agt caa	1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln	
355 360 365	
att tat cca ggg	1116
Ile Tyr Pro Gly	
370	
<210> 112	
<211> 1116	
<212> DNA	
<213> Human Immunodeficiency Virus (HIV)	
<220>	
<221> CDS	
<222> (0)...(297)	
<223> HIV Protease	
<221> CDS	
<222> (298)...(1116)	
<223> Portion of HIV Reverse Transcriptase	
<400> 112	
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg	48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly	
1 5 10 15	
ggg cag cta aag gaa gct cta tta gat aca gga gca gat gat aca gta	96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val	
20 25 30	

tta gaa gaa atg aat ttg cca gga aga tgg aaa cca aaa atk ata ggg	144
Leu Glu Glu Met Asn Leu Pro Gly Arg Trp Lys Pro Lys Xaa Ile Gly	
35 40 45	
gga att gga ggt ttt atc aaa gta aga cag tat gat cag ata ctt gta	192
Gly Ile Gly Gly Phe Ile Lys Val Arg Gln Tyr Asp Gln Ile Leu Val	
50 55 60	
gaa att tgt gga cat aaa gct ata ggt aca gta tta gta gga cct aca	240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Gly Pro Thr	
65 70 75 80	
cct gtc aac ata att gga aga aat ctg ttg act cag att ggt tgc act	288
Pro Val Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Ile Gly Cys Thr	
85 90 95	
tta aat ttt ccc att agt cct att gag act gta cca gta aaa tta aag	336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys	
100 105 110	
cca gga atg gat ggc cca aaa gtc aaa caa tgg cca ttg aca gaa gaa	384
Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu	
115 120 125	
aaa ata aaa gca tta atg gaa att tgt gca gaa wtg gaa aag gaa gga	432
Lys Ile Lys Ala Leu Met Glu Ile Cys Ala Glu Xaa Glu Lys Glu Gly	
130 135 140	
aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gta ttt	480
Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe	
145 150 155 160	
gcc ata aag aaa aaa gac agc act aaa tgg ara aaa tta gta gat ttc	528
Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Xaa Lys Leu Val Asp Phe	
165 170 175	
aga gaa ctt aat aar aga act caa gac ttt tgg gaa gtt caa tta gga	576
Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly	
180 185 190	
ata cca cat ccc gca ggg tta aaa aag aaa aaa tca gta aca gta cta	624
Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu	
195 200 205	
gat gtg ggt gat gca tat ttt tca gtt ccc tta gat gaa gac ttc agg	672
Asp Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg	
210 215 220	
aag tat act gca ttt acc ata cct agt ata aac aat gag acm cca ggg	720
Lys Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Xaa Pro Gly	
225 230 235 240	
att aga tat cag tac aat gtg ctt cca cag gga tgg aaa gga tca cca	768
Ile Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro	
245 250 255	
gca ata ttc caa agt agc atg aca aaa att tta gag cct ttt aga aaa	816
Ala Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys	
260 265 270	
caa aat cca gac ata gtt atc tat caa tac atg gat gat ttg tat gta	864
Gln Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val	
275 280 285	
gga tct gac tta gaa ata ggg cag cat aga aca aaa ata gag gaa ctg	912
Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu	



[illegible]

[illegible]

```
<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400>	114															
cmt	caa	atm	amt	ctt	tgg	car	mra	ccc	cta	gtc	cna	awn	nmm	gkk	agg	48
Xaa	Gln	Xaa	Xaa	Leu	Trp	Gln	Xaa	Pro	Leu	Val	Xaa	Xaa	Xaa	Xaa	Arg	
1				5					10					15		
ggg	gca	aat	aag	gaa	gct	cta	tta	gac	aca	gga	gca	gat	gat	mca	gta	96
Gly	Ala	Asn	Lys	Glu	Ala	Leu	Leu	Asp	Thr	Gly	Ala	Asp	Asp	Xaa	Val	
			20					25					30			
tta	gaa	gaa	atg	wat	tta	cca	gga	aaa	tgg	aaa	cca	aaa	atg	ata	ggg	144
Leu	Glu	Glu	Met	Xaa	Leu	Pro	Gly	Lys	Trp	Lys	Pro	Lys	Met	Ile	Gly	
		35					40					45				
gga	att	gga	ggt	ttt	atc	aaa	gta	agn	cag	tat	gag	cag	ata	ccc	ata	192
Gly	Ile	Gly	Gly	Phe	Ile	Lys	Val	Xaa	Gln	Tyr	Glu	Gln	Ile	Pro	Ile	
	50					55					60					
gaa	atc	tgt	gga	cat	aaa	gct	ata	ggt	aca	gta	ttg	gta	ggm	cct	aca	240
Glu	Ile	Cys	Gly	His	Lys	Ala	Ile	Gly	Thr	Val	Leu	Val	Xaa	Pro	Thr	
65					70					75					80	
cct	gtc	aac	ata	att	gga	aga	aat	ctg	ttg	act	cag	att	ggt	tgc	act	288
Pro	Val	Asn	Ile	Ile	Gly	Arg	Asn	Leu	Leu	Thr	Gln	Ile	Gly	Cys	Thr	
				85					90					95		
tta	aat	ttt	ccc	att	agt	cct	att	gaa	act	gta	cca	gtg	aaa	tta	aag	336
Leu	Asn	Phe	Pro	Ile	Ser	Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	
			100					105					110			
cca	gga	atg	gat	ggc	cca	aaa	gtt	aaa	caa	tgg	cca	tta	aca	gaa	gaa	384
Pro	Gly	Met	Asp	Gly	Pro	Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	
		115					120					125				
aaa	ata	aaa	gca	tta	gta	gaa	att	tgt	aca	gaa	atg	gaa	aaa	gaa	ggg	432
Lys	Ile	Lys	Ala	Leu	Val	Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly	
	130					135					140					
aaa	att	tca	aaa	att	ggg	cct	gaa	aat	cca	tac	aat	act	cca	gta	ttt	480
Lys	Ile	Ser	Lys	Ile	Gly	Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Val	Phe	
145					150					155					160	
gcc	ata	aag	aaa	aaa	gac	agt	act	aaa	tgg	aga	aaa	tta	gta	gat	ttc	528
Ala	Ile	Lys	Lys	Lys	Asp	Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	
				165					170					175		
aga	gaa	ctt	aat	aag	aga	act	caa	gac	ttc	tgg	gaa	gtc	caa	tta	gga	576
Arg	Glu	Leu	Asn	Lys	Arg	Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	
			180					185					190			
ata	cca	cat	cct	gca	ggg	tta	aaa	aag	aaa	aaa	tca	gta	aca	gtg	ctg	624
Ile	Pro	His	Pro	Ala	Gly	Leu	Lys	Lys	Lys	Lys	Ser	Val	Thr	Val	Leu	
		195					200					205				

[illegible]

```
<210> 115
<211> 1116
<212> DNA
<213> Human Immunodeficiency Virus (HIV)

<220>
<221> CDS
<222> (0)...(297)
<223> HIV Protease

<221> CDS
<222> (298)...(1116)
<223> Portion of HIV Reverse Transcriptase
```

<400> 115																
cct	cag	atc	act	ctt	tgg	caa	cga	ccc	ctc	gtc	aca	ata	aag	ata	ggg	48
Pro	Gln	Ile	Thr	Leu	Trp	Gln	Arg	Pro	Leu	Val	Thr	Ile	Lys	Ile	Gly	
1				5					10					15		
ggg	cag	cta	aag	gaa	gct	cta	ata	gat	aca	gga	gca	gat	gat	aca	gtg	96
Gly	Gln	Leu	Lys	Glu	Ala	Leu	Ile	Asp	Thr	Gly	Ala	Asp	Asp	Thr	Val	
			20					25					30			



tta Leu	gaa Glu	gaa Glu 35	atg Met	agt Ser	ata Ile	cca Pro	gga Gly 40	aaa Lys	tgg Trp	aaa Lys	cca Pro	aaa Lys 45	ttg Leu	ata Ile	ggg Gly	144
gga Gly	att Ile 50	gga Gly	ggt Gly	ttt Phe	atc Ile	aaa Lys 55	gta Val	aga Arg	cag Gln	tat Tyr	gat Asp 60	cag Gln	gkg Xaa	ccc Pro	gta Val	192
gaa Glu 65	att Ile	tgt Cys	gga Gly	cat His	aaa Lys 70	gct Ala	ata Ile	ggt Gly	mca Xaa 75	gtw Xaa	tta Leu	ata Ile	ggm Xaa	cct Pro	aca Thr 80	240
cct Pro	gcc Ala	aac Asn	ata Ile	att Ile 85	gga Gly	agg Arg	aat Asn	ctg Leu 90	ttg Leu	act Thr	cag Gln	att Ile	ggt Gly	tgc Cys 95	act Thr	288
tta Leu	aat Asn	ttt Phe	ccc Pro 100	att Ile	agt Ser	cct Pro	att Ile	gaa Glu 105	act Thr	gta Val	cca Pro	gta Val	aaa Lys 110	tta Leu	aag Lys	336
cca Pro	gga Gly	atg Met 115	gat Asp	ggc Gly	cca Pro	aaa Lys	gtt Val 120	aag Lys	caa Gln	tgg Trp	cca Pro	ttg Leu 125	aca Thr	gaa Glu	gag Glu	384
aaa Lys 130	ata Ile	aaa Lys	gca Ala	tta Leu	aca Thr	gaa Glu 135	att Ile	tgt Cys	aca Thr	gaa Glu	atg Met 140	gaa Glu	aag Lys	gaa Glu	gga Gly	432
aag Lys 145	att Ile	tca Ser	aaa Lys	att Ile	ggg Gly 150	cct Pro	gaa Glu	aat Asn	cca Pro	tac Tyr 155	aat Asn	act Thr	cca Pro	gta Val	ttt Phe 160	480
gcc Ala	ata Ile	aag Lys	aaa Lys	aaa Lys 165	gac Asp	agt Ser	act Thr	aaa Lys	tgg Trp 170	aga Arg	aaa Lys	tta Leu	gta Val	gat Asp 175	ttc Phe	528
aga Arg	gaa Glu	ctt Leu	aat Asn 180	aag Lys	aga Arg	act Thr	caa Gln	gat Asp 185	ttc Phe	tgg Trp	gaa Glu	gtt Val	caa Gln	tta Leu	gga Gly	576
ata Ile	cca Pro	cat His 195	cct Pro	gca Ala	ggg Gly	tta Leu	aaa Lys 200	aag Lys	aaa Lys	aaa Lys	tca Ser	gta Val 205	aca Thr	gta Val	ctg Leu	624
gat Asp	gtg Val 210	ggt Gly	gat Asp	gca Ala	tat Tyr	ttt Phe 215	tca Ser	gtt Val	ccc Pro	tta Leu	gat Asp 220	gaa Glu	gac Asp	ttt Phe	agg Arg	672
aaa Lys 225	tat Tyr	act Thr	gca Ala	ttt Phe	acc Thr 230	ata Ile	cct Pro	agt Ser	gta Val	aac Asn 235	aat Asn	gag Glu	aca Thr	cca Pro	ggg Gly 240	720
att Ile	aga Arg	tat Tyr	cag Gln	tat Tyr 245	aat Asn	gtg Val	ctt Leu	cca Pro	cag Gln	gga Gly	tgg Trp	aaa Lys	gga Gly	tca Ser 255	cca Pro	768
gca Ala	ata Ile	ttc Phe	caa Gln 260	tgt Cys	agt Ser	atg Met	aca Thr	aaa Lys 265	ata Ile	tta Leu	gag Glu	ccc Pro	ttt Phe 270	aga Arg	aaa Lys	816
caa Gln	aat Asn	cca Pro 275	gac Asp	cta Leu	gtt Val	atc Ile	tat Tyr 280	caa Gln	tac Tyr	gtg Val	gat Asp	gat Asp 285	ttg Leu	tat Tyr	gta Val	864
gga Gly	tct Ser	gac Asp	tta Leu	gaa Glu	ata Ile	ggg Gly	cag Gln	cat His	aga Arg	aca Thr	aaa Lys	ata Ile	gag Glu	gaa Glu	ctg Leu	912

290	295	300	
aga caa cat ctg ttg aaa tgg ggt ttt acc aca cca gac aaa aag cat			960
Arg Gln His Leu Leu Lys Trp Gly Phe Thr Thr Pro Asp Lys Lys His			
305	310	315	320
cag aaa gaa cct cca ttc ctt tgg atg ggt tat gaa ctc cat cca gat			1008
Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp			
	325	330	335
aaa tgg aca gta cag cct ata gtg ctg cca gaa aaa gac agc tgg act			1056
Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr			
	340	345	350
gtc aat gac ata cag aag tta gtg gga aaa tta aat tgg gca agt cag			1104
Val Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln			
	355	360	365
att tac cca ggg			1116
Ile Tyr Pro Gly			
370			
<210> 116			
<211> 1116			
<212> DNA			
<213> Human Immunodeficiency Virus (HIV)			
<220>			
<221> CDS			
<222> (0)...(297)			
<223> HIV Protease			
<221> CDS			
<222> (298)...(1116)			
<223> Portion of HIV Reverse Transcriptase			
<400> 116			
cct cag atc act ctt tgg caa cga ccc ctc gtc aca ata aag ata ggg			48
Pro Gln Ile Thr Leu Trp Gln Arg Pro Leu Val Thr Ile Lys Ile Gly			
1	5	10	15
ggg cag cta aag gaa gct cta tta gat aca gga gca gat gac aca gta			96
Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val			
	20	25	30
tta gaa gaa ata agt ctg cca gga aga tgg aaa cca aaa ttg ata ggg			144
Leu Glu Glu Ile Ser Leu Pro Gly Arg Trp Lys Pro Lys Leu Ile Gly			
	35	40	45
gga att gga ggt ttt atc aaa gta aag cag tat gat cag ata ccc ata			192
Gly Ile Gly Gly Phe Ile Lys Val Lys Gln Tyr Asp Gln Ile Pro Ile			
	50	55	60
gaa atc tgt gga cat aaa gct ata ggt aca gta tta gta ggm cct aca			240
Glu Ile Cys Gly His Lys Ala Ile Gly Thr Val Leu Val Xaa Pro Thr			
	65	70	75
cct gtc aac ata gtt gga aga aat ctg ttg act cag ctt ggt tgc act			288
Pro Val Asn Ile Val Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr			
	85	90	95
tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag			336
Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys			
	100	105	110
cca gga atg gat ggc cca aag gtt aag caa tgg cca ttg aca gaa gaa			384

[illegible]

<210> 117  
 <211> 1119  
 <212> DNA  
 <213> Human Immunodeficiency Virus (HIV)

<220>  
 <221> CDS  
 <222> (0)...(297)  
 <223> HIV Protease

<221> CDS  
 <222> (298)...(1119)  
 <223> Portion of HIV Reverse Transcriptase

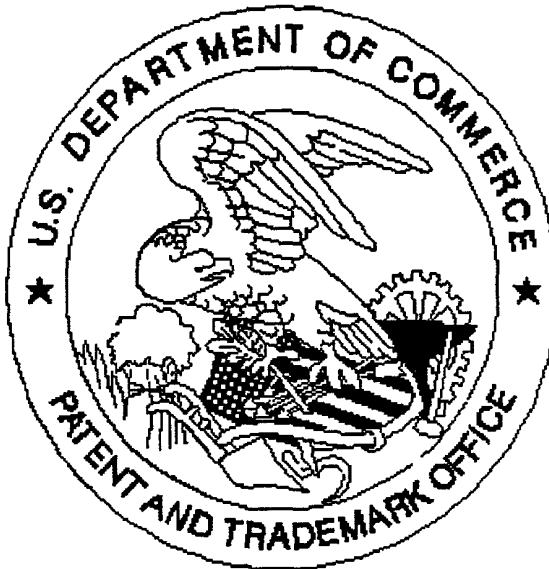
<400> 117  
 cct caa atc act ctt tgg caa cga ccc atc gtc aca ata aag ata ggg 48  
 Pro Gln Ile Thr Leu Trp Gln Arg Pro Ile Val Thr Ile Lys Ile Gly  
 1 5 10 15  
 ggg caa cta aag gaa gct cta tta gat aca gga gca gat gat aca gta 96  
 Gly Gln Leu Lys Glu Ala Leu Leu Asp Thr Gly Ala Asp Asp Thr Val  
 20 25 30  
 tta gaa gaa atg gat ttg cca gga aga tgg aca cca aaa atg ata ggg 144  
 Leu Glu Glu Met Asp Leu Pro Gly Arg Trp Thr Pro Lys Met Ile Gly  
 35 40 45  
 gga att gga ggt ctt gtc aaa gta aga cag tat gat cag ata ccc ata 192  
 Gly Ile Gly Gly Leu Val Lys Val Arg Gln Tyr Asp Gln Ile Pro Ile  
 50 55 60  
 gaa atc tgt gga cat aaa act ata ggt aca gta tta gta gga cct aca 240  
 Glu Ile Cys Gly His Lys Thr Ile Gly Thr Val Leu Val Gly Pro Thr  
 65 70 75 80  
 cct gcc aac ata att gga aga aat ctg ttg act cag ctt ggt tgt act 288  
 Pro Ala Asn Ile Ile Gly Arg Asn Leu Leu Thr Gln Leu Gly Cys Thr  
 85 90 95  
 tta aat ttt ccc att agt cct att gaa act gta cca gta aaa tta aag 336  
 Leu Asn Phe Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys  
 100 105 110  
 cca gga atg gat ggc cca aaa gtt aaa caa tgg cca ttg aca gaa gaa 384  
 Pro Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu  
 115 120 125  
 aaa ata aaa gca tta gta gaa att tgt aca gaa ttg gaa aag gaa gga 432  
 Lys Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Leu Glu Lys Glu Gly  
 130 135 140  
 aaa att tca aaa att ggg cct gaa aat cca tac aat act cca gtg ttt 480  
 Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe  
 145 150 155 160  
 gcc ata aag aaa aaa gac agt act aaa tgg aga aaa tta gta gat ttc 528  
 Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe  
 165 170 175  
 aga gaa ctt aat aag aga act caa gac ttc tgg gaa gtt caa tta gga 576  
 Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly  
 180 185 190  
 ata cca cat cct gca gga tta aaa aag aaa aaa tca gta aca gta ctg 624  
 Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu  
 195 200 205



Ala	Phe	Thr	Ile	Pro	Ser	Arg	Asn	Asn	Glu	Thr	Pro	Gly	Ile	Arg	Tyr
	130					135					140				
Gln	Tyr	Asn	Val	Leu	Pro	Gln	Gly	Trp	Lys	Gly	Ser	Pro	Ala	Ile	Phe
145					150					155					160
Gln	Ser	Ser	Met	Thr	Arg	Ile	Leu	Glu	Pro	Phe	Arg	Lys	Gln	Asn	Pro
				165					170					175	
Glu	Ile	Val	Ile	Tyr	Gln	Tyr	Met	Asp	Asp	Leu	Tyr	Val	Gly	Ser	Asp
			180					185					190		
Leu	Glu	Ile	Gly	Gln	His	Arg	Ala	Lys	Ile	Glu	Glu	Leu	Arg	Gly	His
		195					200					205			
Leu	Leu	Lys	Trp	Gly	Phe	Thr	Thr	Pro	Asp	Lys	Lys	His	Gln	Lys	Glu
	210					215					220				
Pro	Pro	Phe	Leu	Trp	Met	Gly	Tyr	Glu	Leu	His	Pro	Asp	Lys	Trp	Thr
225					230					235					240
Val	Gln	Pro	Ile	Lys	Leu	Pro	Glu	Lys	Asp	Ser	Trp	Thr	Val	Asn	Asp
				245					250					255	
Ile	Gln	Lys	Leu	Val	Gly	Lys	Leu	Asn	Trp	Ala	Ser	Gln	Ile	Tyr	Ala
			260					265					270		
Gly	Ile	Lys	Val	Arg	Gln	Leu	Cys	Lys	Leu	Leu	Arg	Gly	Thr	Lys	Ala
		275					280					285			
Leu	Thr	Glu	Val	Ile	Pro	Leu	Thr	Glu	Glu	Ala	Glu	Leu	Glu	Leu	Ala
	290					295					300				
Glu	Asn	Arg	Glu	Ile	Leu	Lys	Glu	Pro	Val	His	Gly	Val	Tyr	Tyr	Asp
305					310					315					320
Pro	Ser	Lys	Asp	Leu	Ile	Ala	Glu	Ile	Gln	Lys	Gln	Gly	Gln	Gly	Gln
				325					330					335	
Trp	Thr	Tyr	Gln	Ile	Tyr	Gln	Glu	Pro	Phe	Lys	Asn	Leu	Lys	Thr	Gly
			340					345					350		
Lys	Tyr	Ala	Arg	Met	Arg	Gly	Ala	His	Thr	Asn	Asp	Val	Lys	Gln	Leu
		355					360					365			
Thr	Glu	Ala	Val	Gln	Lys	Ile	Thr	Thr	Glu	Ser	Ile	Val	Ile	Trp	Gly
	370					375					380				
Lys	Thr	Pro	Lys	Phe	Lys	Leu	Pro	Ile	Gln	Lys	Glu	Thr	Trp	Glu	Thr
385					390					395					400
Trp	Trp	Thr	Glu	Tyr	Trp	Gln	Ala	Thr	Trp	Ile	Pro	Glu	Trp	Glu	Phe
				405					410					415	
Val	Asn	Thr	Pro	Pro	Leu	Val	Lys	Leu	Trp	Tyr	Gln	Leu	Glu	Lys	Glu
			420					425					430		
Pro	Ile	Val	Gly	Ala	Glu	Thr	Phe	Tyr	Val	Asp	Gly	Ala	Ala	Asn	Arg
		435					440					445			
Glu	Thr	Lys	Leu	Gly	Lys	Ala	Gly	Tyr	Val	Thr	Asn	Arg	Gly	Arg	Gln
	450					455					460				
Lys	Val	Val	Thr	Leu	Thr	Asp	Thr	Thr	Asn	Gln	Lys	Thr	Glu	Leu	Gln
465					470					475					480
Ala	Ile	Tyr	Leu	Ala	Leu	Gln	Asp	Ser	Gly	Leu	Glu	Val	Asn	Ile	Val
				485					490					495	
Thr	Asp	Ser	Gln	Tyr	Ala	Leu	Gly	Ile	Ile	Gln	Ala	Gln	Pro	Asp	Gln
			500					505					510		
Ser	Glu	Ser	Glu	Leu	Val	Asn	Gln	Ile	Ile	Glu	Gln	Leu	Ile	Lys	Lys
		515					520					525			
Glu	Lys	Val	Tyr	Leu	Ala	Trp	Val	Pro	Ala	His	Lys	Gly	Ile	Gly	Ser
		530				535					540				
Pro	Ile	Glu	Thr	Val	Pro	Val	Lys	Leu	Lys	Pro	Gly	Met	Asp	Gly	Pro
545					550					555					560
Lys	Val	Lys	Gln	Trp	Pro	Leu	Thr	Glu	Glu	Lys	Ile	Lys	Ala	Leu	Val
				565					570					575	
Glu	Ile	Cys	Thr	Glu	Met	Glu	Lys	Glu	Gly	Lys	Ile	Ser	Lys	Ile	Gly
			580					585					590		
Pro	Glu	Asn	Pro	Tyr	Asn	Thr	Pro	Ile	Phe	Ala	Ile	Lys	Lys	Lys	Asp
		595					600					605			
Ser	Thr	Lys	Trp	Arg	Lys	Leu	Val	Asp	Phe	Arg	Glu	Leu	Asn	Lys	Arg
	610					615					620				
Thr	Gln	Asp	Phe	Trp	Glu	Val	Gln	Leu	Gly	Ile	Pro	His	Pro	Ala	Gly
625					630					635					640
Leu	Lys	Gln	Lys	Lys	Ser	Val	Thr	Ile	Leu	Asp	Val	Gly	Asp	Ala	Tyr
				645					650					655	
Phe	Ser	Val	Pro	Leu	Asp	Glu	Gly	Phe	Arg	Lys	Tyr	Thr	Ala	Phe	Thr

[illegible]

United States Patent & Trademark Office  
Office of Initial Patent Examination -- Scanning Division



Application deficiencies found during scanning:

☐ Page(s) \_\_\_\_\_ of \_\_\_\_\_ were not present  
for scanning. (Document title)

☐ Page(s) \_\_\_\_\_ of \_\_\_\_\_ were not present  
for scanning. (Document title)

CD-ROM disks containing Tables 4 and 5

☐ *Scanned copy is best available.*